

***United States Court of Appeals
for the Second Circuit***



**PETITIONER'S
REPLY BRIEF**

Original

77-4097

77-4104

UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

Nos. 77-4097 and 77-4104

National Nutritional Foods Association et al.,

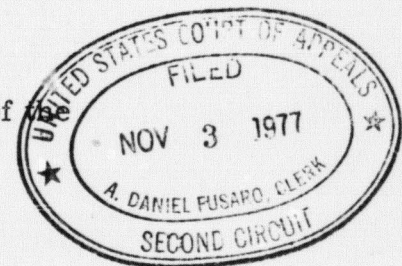
Petitioners

v.

Food and Drug Administration, United States
Department of Health, Education and Welfare, et al.,

Respondents

Petition for Judicial Review of an Order of the
Food and Drug Administration



REPLY BRIEF OF PETITIONER MILES H. ROBINSON

Case No. 77-4104

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IN THE
UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION, et al

Petitioners,

vs.

DONALD KENNEDY, Commissioner of Food & Drugs, and
UNITED STATES DEPARTMENT OF HEALTH EDUCATION &
WELFARE, Food and Drug Administration,

Respondents.

CASE NOS. 77-4097 and 77-4104

REPLY BRIEF FOR PETITIONER MILES H. ROBINSON

I. REPLY TO RESPONDENTS' ARGUMENT THAT
DR. HARPER WAS NOT BIASED (Gov't. Br. pp. 8-11).

Respondents claim that Dr. Harper was not obligated to General Foods because, among other things, he "was a tenured professor at MIT and would have received his salary whether or not General Foods provided a grant to the University" (Gov't. Br. p. 9). The record, however, does not reveal the precise nature of the tenure, which may have protected Dr. Harper only against discharge involving discrimination and not from discontinuation of the grant from General Foods.

The accuracy of Dr. Harper's assertion that he would have been paid regardless of the grant must be weighed in the light of his repeatedly taking self-serving positions which were either unbelievable on their face

or abandoned during cross examination.

Examples of abandoned positions were Dr. Harper's charge of falsehoods committed by Senator Proxmire in his table of changing RDA's (Petitioner's Brief (Pet. Br.) pp. 13-14); Dr. Harper's pretense of concern about consulting for food companies (Pet. Br. pp. 13-14); and his instant rejection of the bar graphs showing similar nutrient requirements dependent on energy intake (Pet. Br. pp. 44-46).

Examples of patently unbelievable self-serving positions were Dr. Harper's denial that sugar is a food (Pet. Br. p. 17); his repudiation of the criterion of optimal health despite its adoption in his own Committee's text (Pet. Br. p. 19); and his dismissal of the value of the nutrient data for animals in the National Academy of Science's (NAS) Booklet No. 10, despite his dependence on this data in his own work (Pet. Br. pp. 47-49).

The timing of the grant at MIT was crucial. Dr. Harper's professorship at MIT and the receipt of the grant occurred in the same year, 1961, and the grant was solely to pay his salary:

DR. HARPER: The General Foods grant amounted to nothing except my salary from the Massachusetts Institute of Technology. (Tr. 32523).

Dr. Harper and respondents would have us believe that neither he nor MIT had any inkling that a General Foods grant given solely to pay Dr. Harper's salary unaccountably appeared on the scene after Dr. Harper became a member of the faculty at MIT.

On the related and touchy subject of General Foods making its \$50,000 grant to Dr. Hoekstra in Dr. Harper's department in the spring of

1975 at just the time Dr. Harper was asked to testify for FDA at the re-hearing (Pet. Br. pp. 11-12), Dr. Harper was asked what conversations he had with General Foods about ~~the~~ s, but he evaded the question:

Q. And did you have any private conversations with General Foods about your department being selected for this \$50,000 grant?

A. I don't understand what you mean by private conversations.

Q. Well, any conversations with General Foods?

A. Certainly they visited all the Universities that were potential places for the placement of this professorship. (Tr. 32526).

In any event, it is clear that negotiations for Dr. Hoekstra's grant began at least six months before his professorship supported by the grant was confirmed. (Pet. Br. pp. 11-12). This is a reasonable sequence of events, and undoubtedly occurred similarly in Dr. Harper's case at MIT, despite his ambiguous assertions aimed at putting a respectable distance between himself and General Foods.

Respondents make much of the theory that the \$50,000 General Foods grant for Dr. Hoekstra's professorship in no way benefited Dr. Harper. (Gov't. Br. pp. 9-10). Ignored is the fact that the grant was given to Dr. Harper's department (Tr. 32525) in which Dr. Hoekstra worked (Tr. 32527). Obviously, Dr. Harper as head of the department will have much control "over the research, essentially, that is supported by this grant" (Tr. 32527), despite Dr. Harper's assertions to the contrary.

With regard to influence from General Foods bearing on Dr. Harper through the Searle-Aspartame connection, respondents do not

dispute the fact (perhaps because it has been in the newspapers) that General Foods put up \$15 million to build an Aspartame plant for Searle, but argue that Searle has no "significant interest in dietary allowances for vitamins and minerals". (Gov't. Br. p. 10). This argument side-tracks the trail between General Foods and Dr. Harper.

First, Dr. Harper is an expert on amino acids, shown by his testimony that he wrote the "protein and amino acid section of the Report" of the RDA Committee*, which is Exhibit P-1165.

Second, the artificial sweetener, Aspartame, is a mixture of two amino acids. (Tr. 32503-04). Dr. Harper is an enthusiastic advocate of Aspartame, and is employed by Searle at \$10,000 a year to help develop the product:

DR. HARPER: I think it would be very appropriate to use it [Aspartame] in foods generally, and I don't see why it should not be used in special dietary foods. (Tr. 32511).

DR. HARPER: I have been a consultant for Searle on some aspects of the development of the product. (0-959, p. 182)**

DR. HARPER: . . . The only conversations I have had with the Searle Company in the last two or three months had to do with studies of the safety of their product. (Tr. 32518).

Other references bearing on Dr. Harper's interest in and expertise regarding Aspartame are found at Tr. 32502-04, 32507, 32510-13,

* Respondents use the term, "Committee", whereas this Court in its earlier decision in this matter (504 F. 2nd at 799) and petitioner's original brief herein use the term, "Board".

** This is from Dr. Harper's address at an NAS Symposium. The full text, pp. 182-195, shows the extent of Dr. Harper's advocacy of Aspartame.

32517-18, 32539-32548, 32559, 32560-64, 32592.

Third, as mentioned earlier, General Foods has put up the money for an Aspartame factory for Searle. (Dr. Harper pleaded ignorance of the "economics" but said, "I know they [General Foods] are planning to use Aspartame and that they have been involved in some way." (Tr. 32517)).

Fourth, Dr. Harper has received at least \$60,000 from General Foods paying for his professorship during four years at MIT. (Tr. 32523, 32525), and General Foods is now contributing \$50,000 a year to his department at Wisconsin in the form of the Hoekstra professorship.

We have here an extensive web of largesse from General Foods, past and present, directly and indirectly benefiting Dr. Harper, and the prospect of the fall-out from a billion dollar business if Aspartame is approved by FDA as an artificial sweetener replacing the cyclamates and saccharine.

Fifth, Dr. Harper admitted that "it is conceivable" he discussed the RDA's with General Foods. (Tr. 32518). But, this minimization must be viewed from the standpoint of his exaggerated efforts to play down any suggestion of conflict of interest. For example, he volunteered that he had never discussed the RDA's with General Foods "on a formal basis, nor had any consulting fee" for doing so. (Tr. 32519). This is certainly leaning over backward in an effort to appear pure. Dr. Harper prides himself on the "guerilla" approach (Pet. Br. p. 13), and it is not at all likely that he would discuss the sensitive matter of RDA's with General Foods on any but a most informal basis.

Finally, it was under Dr. Harper's chairmanship of the 1974 RDA Committee (Tr. 32453-54, 32521) that an extensive and unusual reduction of RDA values took place. (Exhibit 0-957, Addendum (Add.) p. 9a, Table in Senator's Proxmire's speech).*

Respondents unaccountably cling to the erroneous view that cross examination did not force Dr. Harper to retract all his charges against Senator Proxmire. (Gov't. Br. p. 10). Dr. Harper admitted he did not question the accuracy of the figures in Senator Proxmire's Table of RDA's (0-957, p. S10177*, Add. pp.9a).

DR. HARPER: I did not raise a question about the accuracy of the figures themselves. I raised a question about the statement that these all represented recommended dietary allowances. They do not. (Tr. 32822).

Dr. Harper's only charge, as shown in the above quotation, was that the figures were not all from the "recommended dietary allowances", by which he meant exclusively the RDA's of the Food and Nutrition Board (FNB) quadrennial Committee Reports. Therein lies his mistake, now being perpetuated by respondents, because the Table is clearly labelled in its footnotes showing that the RDA's therein are from various sources, including the Committees, the FDA, and independent testimony of Dr. Sebrell, Chairman of the 1968 Committee. The legitimate purpose of the Table displaying this variety was to show the variation exhibited by all authorities taken in concert.

* Petitioner provided Senator Proxmire with this Table, which is essentially a copy of the Table on pp. 1a-2a of the Reply Brief filed in this Court in Lutz et al, Case No. 73-2129. In the Lutz Table the direction of RDA value change is indicated by arrows. The Congressional printer omitted these arrows, so one must deduce from the figures in the Proxmire Table that most of the RDA's therein were reduced.

The petitioner cross examiner, typically, was improperly interrupted by Judge Davidson just as petitioner was bringing out this crucial point by the phrase "or from the Food and Drug or--" (Tr. 32822, emphasis supplied).

Dr. Harper, as can be seen from the whole context of his testimony, is a very alert and intelligent man. It is difficult to believe that before he attacked Senator Proxmire he had not read the Table carefully and understood just where the various RDA's came from according to the descriptions in the footnotes. Or if in his fury at any criticism touching on his powerful Committee of the NAS he failed to notice the origins of the RDA, that failure is additional evidence of his bias or scientific incompetence.

In any event, thanks to Judge Davidson's cue to Dr. Harper to restudy the Table and collect his defence, Dr. Harper asked for and was granted "a 10-minute recess to review this". (Tr. 32822).

When Dr. Harper came back, after a lengthy conference with FDA counsel, he rested his charge only on the RDA's of columns A, C and F of the Table, all of which were the quadrennial recommendations of the FNB Committees, and which by themselves indeed do not constitute a 700% variation in the RDA of folic acid. (Tr. 32823). But Dr. Harper ignored columns B, D and E, which were RDA's from the FDA and from Dr. Sebrell (Chairman of the 1968 Committee) which in conjunction with column F provided the figure of a 700% variation. Specifically, the pregnancy figure in B is 100 mg and in C, D, E and F it is 800 mg, amounting to a variation of

700%. A stated earlier, all columns were clearly identified in the footnotes of the Table. Even after Dr. Harper with counsel had carefully re-studied the Table, he persisted in misinterpreting it in an effort to justify his false accusations against Senator Proxmire. (Tr. 32823). In a last effort, petitioner attempted to bring this out by the following question:

Q. Now, Dr. Harper, that sentence you referred to on page S-10178, does it state that the RDA varied with respect to the recommendations of the Food and Nutrition Board or does it simply state that the RDA varied, period? (Tr. 32824).

FDA counsel's objection to the question was sustained. The answer is given in Senator Proxmire's speech:

"Folacin. The RDA for folacin for some categories of individuals has varied by 700% in the last 10 years."
(Exhibit 0-957, p. S10178, 2nd paragraph, 1st column).

This whole episode is very instructive. It is a devastating example of Dr. Harper's bias or lack of scientific integrity. Even after he recognized his error, he deliberately perpetuated the confusion. Similarly, it is a clear example of Judge Davidson's bias or lack of judicial integrity. Whenever the cross examiner touched a crucial nerve, he stepped in to make elucidation as difficult as possible. These constitute formidable obstacles in the path of the Commissioner and his advisors receiving the information they should have to protect the nutrition of the public.

In conclusion on the issue of bias, Dr. Harper was unquestionably subject to pressure from General Foods through the Aspartame connection.

It was to his advantage to keep a long established train of financial favors from General Foods coming his way, by tilting the RDA's toward lower values most favorable to the interests of that giant corporation and other members of the food industry. The egregious use of incompetent statistics, the indifference to the "red flag" evidence of primate nutrition compiled by the NAS, the intemperate and wholly unjustified attack on Senator Proxmire, and the attitude of guerilla warfare against Adelle Davis are all best explained by a deep seated bias of Dr. Harper, Chairman of the RDA Committee of the NAS Food and Nutrition Board.

II. REPLY TO RESPONDENTS' ARGUMENTS REGARDING
"ADEQUATE" HEALTH (Gov't. Br. p. 11), USE OF
ANIMAL DATA (Ibid. pp. 18-20), AND RDA OF VITAMINS
A, D, E AND C (Ibid., pp. 20-21).*

With regard to their preference for "adequate" as opposed to "optimum" health, Dr. Harper and the Board Committees are looking backward, in Dr. Harper's words "hopefully" to what is "adequate" (Tr. 32572), not forward to the optimum which might reduce the national health bill of \$160 billion a year.

Respondents cite Dr. Harper's assertion that there is "no evidence that increased amounts that are recommended do anything to improve health". (Gov't. Br. p. 11). One does not see evidence when it is not looked for.

* These sections of petitioner's principal brief contain the following typographical errors: p. 45, 10th line from bottom "of species" should be "or species"; p. 51, line 2, "vitamin A" should be "vitamins A and D".

For example, respondents defend Dr. Harper's reliance on the criterion of night blindness to detect deficiency of vitamin A, while excluding the criterion of levels of vitamin A in the liver. "While he wasn't certain, he thought it was highly probably [sic] that night blindness would be one of the first discernible symptoms of vitamin deficiency". (Gov't. Br. p. 21).

In sharp contrast to Dr. Harper's uncertainty and hopeful speculation on this important matter, we see the Canadians moving forward, checking vitamin A levels in the liver, and expressing concern at how low they are. (Pet. Br. p. 55). The questions of whether liver biopsies have been performed in vitamin A deficiency, or when very large amounts of vitamin A in the liver signify toxicity (Gov't. Br. p. 21) are merely red herrings across the trail. What matters is that Canadian public health scientists are not content with the old standard of night blindness and now include the criterion of liver levels. Whereas, Dr. Harper is so disinterested in this subject that he did not know that the textbook he uses in his classroom describes a level of vitamin A in the liver seven times higher in some populations as compared to others. (Tr. 33429, Pet. Br. p. 55).

When Dr. Harper threw the red herring of toxicity on this trail, petitioner tried to bring the testimony back to the real issue by asking Dr. Harper if it was not true that "blood serum levels of vitamin A hold up even though the liver may be totally exhausted of vitamin A". (Tr. 33430). The answer to this question would have refocussed attention on the physiological flux of vitamin A in the liver as distinct from pathological

accumulations. But Judge Davidson did not permit the question, stating that the mandate of this Court did not give the right to inquire into the scientific background by which the RDA levels were set "in the same detail with respect to each and every vitamin or each and every nutrient." (Tr. 33431).

This ruling was clearly erroneous. Again, it is typical of Judge Davidson's bias and improper interference with the cross-examination, which repeatedly shielded Dr. Harper and blocked the necessary airing of the scientific issues.

With regard to the experimentally proved need of rats for 19 times more vitamin A when pregnant, and Dr. Harper's assertion that the pregnant human needs only 3 times more (Gov't. Br. p. 21), Dr. Harper summarized his justification of the discrepancy on the grounds that the human female, even if she is having a baby as often as she can, is not working as hard as a rat. (Tr. 33438). He depended on his calculations involving only the frequency of pregnancy and the ratio of offspring to maternal weight. (Gov't. Br. p. 21).

Respondents do not make clear that these calculations are mere afterthought speculations by Dr. Harper. When specifically asked if the 19 to 1 ratio held for man, he earlier had stated, "I do not know the answer to your question". (Tr. 33433-34). On their face, the calculations represent too narrow a criterion. Given the universal efficiency of biological processes, and taking into account the complexity of human structure as compared to the rat, it is irrational to believe maximal reproductive

activity requires more work (energy) in the rat than in the human.

With regard to the Committee's failure to distinguish between artificial vitamin D₂ and natural vitamin D₃, despite the evidence from monkeys that the artificial form may permit decalcification of bones which at the same dose the natural form prevents (Pet. Br. pp. 55-56), respondents rely on Dr. Harper's statement that on a visit to California he talked over "this very problem" with Dr. Alfin-Slater* and found" no evidence to suggest that we should specifically designate vitamin D₃ in the RDA Bulletin" (P-1165). (Tr. 33472, Gov't. Br. pp. 21-22).

Here again, whether experts find evidence depends on whether they really are experts and whether they really look for the evidence. Dr. Harper claims he went into the matter thoroughly with Dr. Alfin-Slater (who was "the Committee member on the Board responsible for determining the RDA for this vitamin" (Gov't. Br. p. 22)), but Dr. Harper was not enough interested in the matter to notice the hazards to monkeys of artificial vitamin D₂ described in the National Academy of Science's authoritative Booklet No. 10, (0-936, p. 35, Add. 15a-16a), a publication Dr. Harper depends on for his own nutritional research (Tr. 32898, Pet. Br. p. 47). What this comes down to is the question of Dr. Harper's scientific competence in human nutrition.

Under voir dire, plaintiff brought out that "the great majority" of Dr. Harper's research was done on rats. (Tr. 32482). Dr. Harper is not

* Misspelled in the transcript as "Alpenslater".

a medical doctor (P-1164), so it is reasonable to assume that in extrapolating nutritional experience from rats to humans a competent non-medical nutritionist would not ignore authoritative evidence from the most important and closest animals to man, which are the monkeys and other non-human primates. This is especially true because the FNB Committee is depended substantially on animal evidence due to the dearth of evidence from human experiments:

DR. HARPER: What we have is scanty information on human experimentation. (Tr. 32672. See also references in Pet. Br. pp. 40-43, 45).

In summary, Dr. Harper's assertions that he adequately discussed the hazards of artificial vitamin D₂ with Dr. Alfin-Slater and other unnamed experts are negated by his own actual disinterest and ignorance on this subject. We may assume the same is true of Dr. Alfin-Slater, since she apparently did not know or care about the monkey data either. In any event, the two of them did not discuss it, since Dr. Harper had never heard of it prior to his cross-examination.

This situation is a good example of why petitioner should be permitted to bring in experts on rebuttal who are not tainted with the commercial bias of Dr. Harper, experts who are deeply concerned about human nutrition and who are not distracted by the pursuit of false nutritional gods such as the artificial sweeteners. It is difficult to be really interested in what artificial vitamin D₂ can do to monkeys, or in other upsetting information from the animal world of grave import to human nutrition, when one is locked into the billion dollar prospects of Aspartame. The natural

tendency under these circumstances is to favor a humdrum nutritional status quo, especially if that is also agreeable for other reasons to the powerful promoters of Aspartame.

Part of maintaining this status quo was Dr. Harper's intemperate attacks on Senator Proxmire and Adelle Davis. These appear aimed at discouraging the public from finding out for itself what the experts in power have not yet cared enough about to discover. A shrewd, caring, searching layman working every day on his diet with the help of someone like Adelle Davis is likely to discover more useful nutritional information than a biased, uncaring professional whose bread is buttered by a giant corporation in the food industry.

With regard to elucidating the methodology for the RDA of vitamin C, respondents ignore the full course of the attempt to cross examine, in which Dr. Davis withdrew his original approach aimed at probing merely the drop in the RDA from 1968 to 1974. (Gov't. Br. p. 22). From that point on, Judge Davidson's (ALJ) rulings were so contradictory and confusing that it was impossible for Dr. Davis to proceed.

Tr. 33411, lines 16-22, Add. 17a: ALJ seems to rule out any attack on the scientific basis for the present (1974) RDA, but by not qualifying his last mention of the word, RDA, leaves the issue dangling.

Tr. 33412, lines 15-23, Add. 18a: ALJ restricts inquiry to methodology of 1968 RDA's, yet states he did not rule out an inquiry "about the scientific basis of the 1974 RDA's."

Tr. 33413, lines 10-22, Add. 19a: ALJ draws a strange distinction between allowing inquiry about methodology, versus scientific papers that describe that methodology. Again he rules out studies subsequent to 1968, together with an obscure reference to what would be relevant after 1968: "the result of that is something I have ruled out."

This contradictory backing and filling took unfair advantage of Dr. Davis. Finally, Judge Davidson presented Dr. Davis with an impossible task: to inquire into the scientific basis of the 1974 RDA for vitamin C, but not to cross examine Dr. Harper on the scientific studies which constitute that basis as described in the 1974 report, among which were the Hodges and Baker studies (P-1165, p. 64), with which Dr. Davis' first question was concerned. (Tr. 33412).

Respondents support only the restriction on questions directed at the difference between the 1968 and 1974 levels of the RDA, and not on the methodology of the 1974 RDA. Dr. Davis said he could have avoided the former while accomplishing the latter, but Judge Davidson denied him the opportunity. Petitioner submits that this was prejudicial error.

If it should be argued that petitioner had no right to go into even the methodology of the 1974 RDA, petitioner would be placed in the unreasonable position of being denied cross examination of Dr. Harper on the 1974 methodology for which as Chairman of the Committee he was responsible, but allowed to cross examine him on the 1968 methodology with which he had nothing to do.

Such a predicament conflicts with the Commissioner's stated recognition of the ongoing and dependent relationship between the U. S. RDA's and the regular reports of the Committee's RDA's:

"... it is reasonable to anticipate changes in the existing U. S. RDA's to reflect changes in the NAS/NRC RDA's when the latter are next published." (41 Fed. Reg. p. 46164, bottom of col. 2, Oct. 19, 1976, emphasis supplied. See also Part 80.1 (d)(2) of the regulations, Ibid., p. 46172, col. 1, Add. 20a-21a).

Beyond that, it is not good science or in the public interest, or, one hopes, good law to confine the inquiry to out-of-date methodology. FDA was given the privilege by this Court of presenting a surrogate witness to atone for its "blatantly erroneous restriction" of petitioner's original cross-examination. It would be a redoubling of the privilege to FDA and a redoubling of the injury to petitioner to deny cross examination of the surrogate witness on the subject of what he personally knows about the ongoing methodology now culminated in the 1974 RDA's.

Petitioner submits that Dr. Harper should be brought back for that interrogation, and that petitioner should be permitted to bring on rebuttal witnesses, so that the Commissioner may be fully informed by unbiased experts of the defects in the methodology by which the RDA of vitamin C has been determined.

III. REPLY TO RESPONDENTS' ARGUMENT THAT THE BOARD'S STATISTICAL METHODOLOGY WAS SCIENTIFICALLY SOUND (Gov't. Br. pp. 15-18). *

Respondents argue that Dr. Harper established that it was reasonable for the Committee to adopt a coefficient of variation of 15%, but he could not substantiate this claim under cross examination. First, he admitted that there are some experts "who feel that the range of variability is much in excess of this". (Tr. 32674).

Second, Dr. Harper was asked where in the Committee's 1974 Report (P-1165) was there any reference to substantiate the use of the 15% coefficient. (Tr. 33132). Dr. Harper cited several references (Tr. 33132), but had to admit that they only referred to the "statistical use of coefficients of variation", not to a substantiation of using the figure of 15%. (Tr. 33134).

Dr. Harper then retreated to Dr. Davis' having earlier supplied "a reference yourself indicating that it ranged between 10 and 30% " for protein, and claimed that there was only one set of values that approached 20%. (Tr. 33134).

Dr. Davis then attempted to pursue this claim, pointing out that in the books Dr. Harper was referring to there were no citations substantiating the use of 15%. (Tr. 33135).

At this point, Dr. Davis was hot on the trail of Dr. Harper's arbitrary use of the 15% figure which Dr. Harper could not substantiate

* The statistical section of petitioner's principal brief contains the following typographical errors: p. 28, 7th line from bottom, "10 + 1.5 = 13 mg" should read "10 mg + 1.5 mg + 1.5 mg = 13 mg"; p. 31, line 11, "made" should be "met".

from the scientific literature, but at this crucial juncture Judge Davidson stopped the cross examination on the grounds that the matter had been adequately explored in previous days..

DR. DAVIS: I am trying to find out where this number 15 percent comes from.

JUDGE DAVIDSON: I am glad you told me that, because if you told me that a long time ago, I would have told you to forget it, because we went into that either yesterday or the day before. The doctor explained they used the 15% and how they arrived at it. If you are not happy with the way he did it, you have everything you need. His testimony is of record. (Tr. 33135-36).

In thus blocking the inquiry, every statement Judge Davidson made in this exchange, except the last sentence of no consequence, was essentially false. First, it is perfectly clear from the record that Dr. Davis was pursuing the 15% figure, and Judge Davidson was perfectly aware of this. Second, the matter was not adequately gone into on previous days, but consisted only of preliminary information from Dr. Harper about where he got the 15% (Tr. 32612) and a mere assertion that the figure was reliable made to a different cross examiner, Mr. Ullman (Tr. 32673). Dr. Davis had every right to check out this information and assertion overnight and probe into it on a subsequent day. When stopped in his cross examination, Dr. Davis did not at all "have everything" he needed. He lacked the only thing that mattered, the proof that texts cited by an evasive witness did not support use of the 15% coefficient of variation which the witness had said they did. Petitioner submits that it was prejudicial error to stop the cross examination at this crucial juncture.

With regard to the 1974 Committee's abandonment of the 38% coefficient for vitamin C, we have only Dr. Harper's assertion that his Committee had "more reliable information than had been available earlier" (Tr. 33136). Since Judge Davidson ruled out inquiry into the 1974 methodology of the vitamin C RDA (¹⁴⁻¹⁵supra, pp.), this alleged reliability could not be tested. As it was, in answer to a direct question, Dr. Harper did not deny that the 1968 use of the 38% figure raised some questions about the 1974 use of 15%. (Tr. 33137).

Respondents argue that Dr. Harper never in actual words testified that a non-Gaussian distribution was applicable to RDA's (Gov't. Br. p. 16). This develops the unessential. It is enough to have Dr. Harper's admissions (Pet. Br. pp. 29-30) that we really do not know the shape of the curve out in the crucial region of two standard deviations above the mean (Tr. 33041), which means we do not know that it is Gaussian; that in the one (Beaton) reference in the 1974 Report discussing curves, Dr. Harper is not sure the curve is Gaussian (Tr. 33040); and that none of the Board's reports cite evidence that the curves are Gaussian for any nutrient. (Tr. 33038).

Respondents state that the use of the Gaussian hypothesis has been successfully tested, referring to Tr. 33045-46. (Gov't. Br. p. 16, item (5)). Dr. Harper makes this assertion at the bottom of Tr. 33045, and supports it in his preceding answer by two examples of satisfactory nutrition developed from "information about requirements and recommended dietary allowances": first, laboratory animals maintained for many generations; and second, humans maintained on intravenous solutions. (Tr. 33045, lines 2-15).

Having elsewhere relegated animal requirements to the bottom of the scale of significance to human requirements, especially with respect to the bar graphs comparing animals with man (0-931), Dr. Harper now raises them to premier significance as a test of using strict Gaussian curves for human requirements.

And what are these animal requirements which Dr. Harper now brings forward to support his statistical methodology? The best animal evidence is from the NAS Booklet No. 10 (0-936, summarized in the bar graphs, Add. 22a-23a), which Dr. Harper uses in his own work, but which he rejects as irrelevant to human requirements, especially the fact that this animal evidence for the animal closest to man, the monkey, shows far higher needs by the accepted criterion of the common denominator of energy intake for just those nutrients which currently are the most controversial (Pet. Br. p. 51). Dr. Harper wants to have it both ways, but he is hoist by his own petard. In trying to defend his statistical incompetence, he has only succeeded in destroying his defence against the red flag animal evidence of the bar graphs in 0-931.

In his extremity under Dr. Davis' cross examination, Dr. Harper went so far as to abandon the utility of statistical distribution curves:

DR. HARPER: What I am trying to point out is that the shape of the distribution curve may have very little to do with it. . . (Tr. 33045).

Little needs to be said about Dr. Harper's extreme example of humans nourished solely by intravenous solutions for as long as a year. (Tr. 33045, lines 14-15). Dr. Harper soon had to admit that some of the solutions "contain more" than the RDA's (Tr. 33047, line 8), and we know nothing about the criteria of health involved. We know only that Dr. Harper's criteria are low; for example, no more than a major illness every few years, and not visibly stunted. (Pet. Br. p. 19).

With regard to the Committee's failure to consider the statistical significance of the simultaneous need for all nutrients, respondents cite reference to Tr. 33082, 33109-11, and 33117 to prove that this "statistical problem" was nothing more than an unlikely hypothetical. This is a complete mischaracterization of the record. At Tr. 33081, lines 9-10, Dr. Harper says we don't have the information to assess this particular statistical probability. This statement ignores and second-guesses the very function of statistics as he himself uses it in producing RDA's, which is to take what nutritional data one has and give it the mathematical treatment of statistics. One does not cut off elementary and imperative steps (0-932 A-D, Add. 24a-27a) in establishing a statistical probability just because one wishes there were more experimental data with which to work. The function of statistical methodology is to alert one to the shortcomings of the data and to come up with answers that allow for them.

At Tr. 33082, lines 5-7, Dr. Harper agrees that the probability of unmet needs goes up if simultaneous multivitamin needs are considered, but through Tr. 33109-11, Dr. Harper contradicts his earlier assent, and

simply denies the proposition (Tr. 33109, line 24); adding later that it is hypothetical. (Tr. 33111, lines 24-25). A little later we find that in an effort to avoid the simple statistical treatment of simultaneous multivalent need, Dr. Harper is prepared in effect to dispense with statistics, agreeing that the proposition is true only "If you want to put this in terms of a statistical distribution. . ." (Tr. 33117, lines 1-9).

That this discard of statistics was indeed his intention is fully confirmed a little later when he says that when food was fortified against pellagra (over 30 years ago):

DR. HARPER: . . . they did not have to go through all this statistical manipulation. . . it was done without all of this kind of statistical manipulation." (Tr. 33119, lines 17-18, 24-25).

We may conclude that when Dr. Harper and the prestigious NAS/NRC/FNB Committees want to impress the unsuspecting public, they are most weighty and prolific with their repeated mention of statistical justification for the RDA's in their quadrennial reports. But when the Chairman of such a Committee is hauled up on the carpet, he will throw statistics to the winds to cover up his perversion of their use. We may also conclude that Dr. Harper is a much more wily than objective scientist.

Judge Davidson's contribution to enlightenment in the struggle over simultaneous unmet needs was to accuse Dr. Davis of arguing and of asking a leading question when ^{Dr. Davis merely} clarified a question naming the particular year of a FNB statement (Tr. 33118, lines 7-19); and to cue the witness to answer that the proposition put forward by Dr. Davis was irrelevant. (Tr. 33119, lines 3-13, Add. 28a-30a).

IV. REPLY TO RESPONDENTS' ARGUMENT OF NO ERROR
IN JUDGE DAVIDSON'S PROCEDURAL RULINGS
(Gov't. Br. pp. 22-26)*

From the examples in petitioner's principal brief and reply brief... it is obvious that Judge Davidson did not dispense even-handed justice in the rehearing. Respondents have searched the record and have come up with a few instances where Judge Davidson was considerate of petitioner in matters of small significance. The difficulty respondents had in claiming this treatment is well exemplified by the two instances they found purporting to illustrate petitioner's satisfaction with Judge Davidson's conduct of the hearing. The first was a charitable and soon regretted expression of hope by petitioner that Dr. Davis would be fairly treated. (Tr. 33029). The second was after petitioner had been cross examining for 3 hours on the last day that the witness was on the stand; and petitioner in response to a question raised about going on for another day, was merely making it clear in the rather unguarded language of fatigue that he could have no objection to obeying the immutable laws of relevance, materiality and repetition. (Tr. 33362). Implicit in that statement was that when Judge Davidson was obeying these laws he was being fair, otherwise not.

V. CONCLUSION

The Agency has not complied with the remand instructions of this Court, nor with federal and other rules of fair administrative proced-

* The section of petitioner's principal brief dealing with this subject contains a typographical error on p. 60: the word, "even" should be deleted.

Original

ure. Petitioner should be permitted to cross examine Dr. Harper on the methodology used by the 1974 Committee in determining the RDA of vitamin C, and to present rebuttal witnesses with respect (1) to the RDA of vitamin C; (2) the statistical methodology used for determining the Committees' 1968 and 1974 RDA's; and (3) the significance of animal requirements, including data from the NAS, to the human RDA's.

Petitioner respectfully prays that the orders of the FDA dated October 19, 1976, and April 19, 1977, adopting certain levels of the U. S. RDA's, be permanently set aside, and for such other relief as this Court may deem appropriate.

Miles H. Robinson

Miles H. Robinson, M. D.
Petitioner pro se, No. 77-4104

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October 26, 1977

CERTIFICATE OF SERVICE

I hereby certify that four copies of the Reply Brief of Petitioner, Miles H. Robinson (No. 77-4104), have this date been served by first class mail on Charles R. McConachie, Chief, Consumer Affairs Section, Anti-trust Division, U. S. Department of Justice, Washington, D. C. 20530, Attorney for Respondents, and one copy on Milton A. Bass, 747 3rd Avenue, New York, New York 10017, Attorney for National Nutritional Foods Association, et al.

Miles H. Robinson

Miles H. Robinson

Dated: October 26, 1977

ADDENDUM

CITIZENS FOR HEALTH INFORMATION, INC.
10120 CHAPEL ROAD
POTOMAC, MARYLAND 20854

ADDENDUM, page 1a

Exh. D-959

SWEETENERS

Issues and Uncertainties

ACADEMY
FORUM
Fourth of a Series

NATIONAL ACADEMY OF SCIENCES

WASHINGTON, D.C.
1975

ASPARTAME

Alfred E. Harper

I have been asked to talk about aspartame, a new type of sweetener that has been developed and tested by the G. D. Searle Company. It was approved by the Food and Drug Administration in 1974 for use in a number of food systems. I have been a consultant for Searle on some aspects of the development of the product.

My objective is to tell you what aspartame is, what properties it has that make it a useful sweetening agent, how it is utilized or metabolized by the body, what limitations it has as a sugar substitute, and how it has been examined to assure that consumption of foods sweetened with it will not pose a hazard to health (1,2,3).

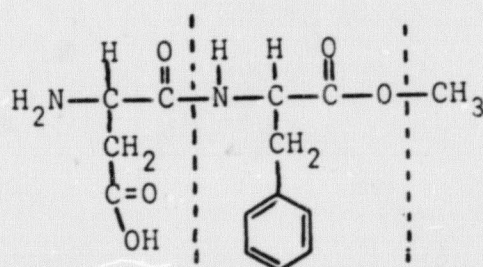
Aspartame is the methyl ester of the dipeptide, L-aspartyl-L-phenylalanine (Figure 1). The constituents of aspartame occur naturally in foods. Aspartic acid and phenylalanine are amino acids that are present in all food proteins. Aspartic acid is a nutritionally dispensable amino acid. If it is not provided in a diet, the body can synthesize it from glucose and ammonia or from other amino acids. Phenylalanine is a nutritionally essential or indispensable amino acid; that is, the body cannot synthesize it. For normal body function, phenylalanine, like any other essential nutrient, must be provided preformed in the food. Methyl esters are common constituents of plant products, especially of substances that impart flavors in fruits and vegetables, juices, and liquors.

Aspartame is a white, odorless, crystalline powder that is soluble in water, more soluble in acid than in neutral solutions, and, as is usually the case, more so in warm than in cold solutions. Aspartame is about 200 times as sweet as sugar in taste tests. Its flavor has the characteristics of sugarlike sweetness, and it has no aftertaste. It also has the property of enhancing the flavors of certain foods, especially those with fruit flavors.

Aspartame is stable in dry form and can be stored in closed containers at 40 degrees centigrade, that is 104 degrees Fahrenheit, for over one year with little deterioration, and the test is still continuing.

When aspartame decomposes, it loses the methyl of the methyl ester, leaving the dipeptide L-aspartyl-L-phenylalanine (Figure 2). This has a tendency to lose water and cyclize to form the diketopiperazine of

ASPARTAME



L-aspartyl-L-phenylalanine
methyl ester (molecular weight
294.3)

FIGURE 1

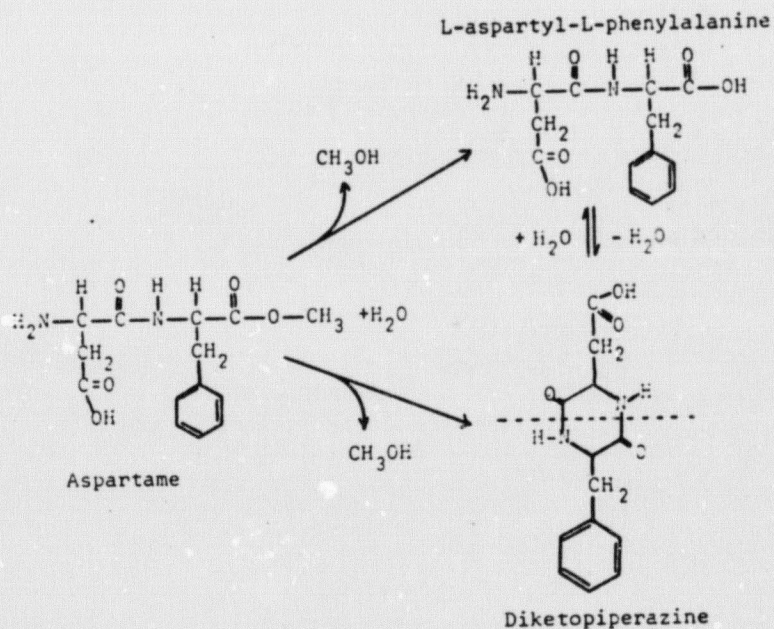


FIGURE 2

the dipeptide. This conversion occurs slowly in acidic solutions and much more rapidly in alkaline solutions. When sugar decomposes, the products formed initially are as sweet as sugar itself. Aspartame, however, loses its sweetness when it undergoes this type of decomposition.

In a solution at pH 4, that is about the acidity of root beer, stored at room temperature, 68 degrees Fahrenheit or 20 degrees centigrade, 20 percent of the sweetness of aspartame would be lost after 4-1/2 months. In Table 1 are summarized some observations on the time for loss of 20 percent of sweetness in relation to the temperature of storage. Twenty percent of sweetness is about the amount of loss that becomes detectable in a comparative taste test. In a neutral solution, of course, even at room temperature, half of the sweetness would be lost in a matter of hours. Therefore, although aspartame can be substituted for sugar and for tabletop use in dry products, such as sweetened powders for beverages and in puddings and fillings that do not require extensive cooking, it is not suitable for sweetening most alkaline or neutral products that require high-temperature baking, broiling, or frying; nor is it suitable for sweetening nonacid products in solution that will be stored for long periods of time.

Its stability in all foodstuffs has not been completely explored as yet, and there may be some interactions that increase its stability. Nevertheless, this means that aspartame is not a general substitute for sugar. Also, of course, it replaces only the sweetness and not the bulk, the preservative properties, or textural properties of sugar.

TABLE 1 Effect of Temperature on the Time for Loss of 20% of the Sweetness of Aspartame in Acidic Solution (pH 4.0)

Storage Temperature (°C) ^a	Time for 20% Decomposition (days)
10	387
20	134
30	51
40	22
55	5
68	2
80	1

^a20°C = 68°F; 40°C = 104°F.

On the other hand, because of the amount of aspartame required to impart sweetnesses is so small, it will have some unique uses for which sugar is not suitable, such as to sweeten foods that now cannot be sweetened with sugar because the large amount of sugar required alters some critical property.

How does the body handle aspartame? As peptides and esters are normal constituents of foods, one would expect the peptide and ester bonds of aspartame to be split by the enzymes, the peptidases and esterases of the digestive tract -- just as are the peptides and esters of food products -- and that these products would be absorbed and utilized just as they are when they are consumed as constituents of foods.

The results of metabolic studies with isotopically labeled aspartame in rats, dogs, monkeys, and in man support this assumption. Unchanged aspartame was not detected in blood plasma after the administration of aspartame to subjects, but free aspartic acid and phenylalanine were. By using aspartame labeled with an isotope specifically in each one of its constituents -- the methyl group, the aspartic acid, and the phenylalanine -- the ultimate fate of each of these could be examined in animals.

The formation of carbon dioxide, the end product of oxidation of each of these substances in the body, followed essentially the same time course, whether the amino acids or the methanol were administered individually or whether they were administered in aspartame.

Since aspartame is metabolized in the body in the same way as amino acids, unlike saccharin and cyclamates, it is a nutritive substance. Weight for weight, it should yield the same amount of energy as carbohydrates or proteins. Being a peptide, one would expect it to behave as proteins do and provide 4 kilocalories per gram. However, because it is required in only minute amounts to sweeten foods, with a sweetening power of 200 times that of sugar, it will still contribute only negligibly to total energy intake when providing sweetness. Because it is a nutritive substance, aspartame has not been classified as an artificial sweetener, so this means that its use will not be restricted to special dietary foods.

As the diketopiperazine of L-aspartyl-L-phenylalanine can form during the storage and preparation of the product or of foods containing it, the metabolism of this product also has been examined. It is not highly soluble, and it is biologically rather inert. When it is injected directly into a vein, it is excreted unchanged in the urine. When it is fed to germ-free rats, it is not metabolized. However, from studies on animals with the usual intestinal flora, evidence was obtained that intestinal microorganisms can split the diketopiperazine to give aspartic acid and phenylalanine and some metabolites of these.

The safety studies that have been conducted on aspartame and its diketopiperazine derivative were reviewed in a symposium held last November (3), so I shall mention only briefly the types of studies that have been done.

It is important in assessing safety studies to remember that there is a toxic level for most, if not all, nutrients and other chemical

compounds. Safety studies are not undertaken to determine whether or not a substance can induce an adverse or toxic reaction, but to determine what amount is required to cause adverse effects or toxic reactions, and to ensure that the level of use will be well below what is found to produce such effects or reactions.

In biological studies in which dosages of aspartame greatly in excess of the projected consumption levels were administered to animals (gram per kilogram of body weight quantities compared to projected intakes are in the order of milligram per kilogram of body weight quantities), no adverse effects were observed in the cardiovascular, gastrointestinal, endocrine, reproductive, or central nervous systems. In rats, with extremely high doses of 4 grams per kilogram of body weight, mild behavioral changes and food intake depression occurred. Similar effects were observed after administration of comparable amounts of L-phenylalanine in the free form. In monkeys, no effects were observed with 1 gram per kilogram of body weight. Some monkeys receiving 3 grams per kilogram of body weight showed a type of seizure. This is about 300 times the anticipated intake level. Similar observations were made by these same investigators using phenylalanine at comparable levels.

3 g./kg
is 300 x expected
use

Both aspartame and the diketopiperazine have been tested for toxicity in the chronic and acute studies in several species of animals, again at levels greatly in excess of anticipated ingestion levels, levels of from 2 up to as high as 8 grams per kilogram of body weight, versus anticipated ingestion levels of 10 to 20 milligrams per kilogram of body weight. Both have been tested for their ability to cause tumors, malformation of the fetus, and mutations. Studies have been conducted with human volunteers to assess the tolerance of normal, obese, and diabetic individuals for aspartame. In none of these tests was evidence of adverse effects from either compound obtained except when the amount administered was sufficiently high to provide enough phenylalanine to retard growth. Adverse effects have long been known to occur in animals consuming excessive amounts of several essential amino acids, among them phenylalanine. Some of these tests are continuing.

What are the specific concerns with aspartame? It contains phenylalanine, which cannot be degraded by individuals with the genetic defect of phenylalanine metabolism, phenylketonuria. One child in 10,000 is born with this defect, about 400 infants a year. The disease is detected by a screening program that is required by law in all but seven states. If infants with this disease are to develop normally, their intake of phenylalanine must be restricted, just as diabetics, who make up probably 1 to 2 percent of the total population, must restrict their intake of sugar, and individuals with many types of kidney disease must restrict their intake of protein.

Aspartame will therefore be labeled to indicate that it contains phenylalanine, so that if it is used in the diets of individuals with phenylketonuria, the amount consumed can be included as part of their allowed allotment of phenylalanine. One person in 70 carries the recessive gene for phenylketonuria. These people show no abnormalities, but

may have greater than normal elevation of blood phenylalanine concentration after ingesting foods rich in phenylalanine.

In tests that were done on a group of such people over a period of six weeks when they consumed as much as 8 grams of aspartame per day -- between 10 and 20 times the amount they would be likely to ingest, or 3 to 5 times the average anticipated daily intake in a single dose -- no abnormal reactions were noted, nor was there evidence of prolonged or unusual elevations of blood phenylalanine concentration.

Another possible concern is with the aspartic acid provided by aspartame. Glutamic acid and aspartic acid administered in very large single doses, 1 gram or more per kilogram of body weight, to newborn rodents will produce lesions in the hypothalamus, an area of the brain, that will result in obesity.

In lifetime studies in rats in which up to 400 times the anticipated use level of aspartame, about 8 grams per kilogram of body weight per day, was administered to pregnant females in their diet, and then subsequently to their offspring in a lifetime study, although the brains were not examined in this study, no physical abnormalities were observed in the offspring. Doses of aspartame in amounts found to cause brain lesions in newborn mice were not found to cause such lesions in neonatal monkeys, even when combined with glutamate. In human studies in which subjects were administered 34 milligrams of aspartame per kilogram of body weight, no elevation of serum aspartic acid was observed. A pint of milk in a single feeding would provide about 6 grams of aspartic acid and glutamic acid.

What about the probable consumption of aspartame? Average sugar consumption generally, as we have discussed several times, is between 100 and 150 grams a day, so not more than 0.5 to 0.8 grams of aspartame would be required to provide sweetness equivalent to all of this. Because aspartame is not suitable as a replacement for sugar in some foods, such as products that are neutral in reaction and must be baked at high temperature or liquids that are neutral in reaction and have to be stored, average consumption of aspartame should not exceed half a gram per day.

This would provide 280 milligrams of phenylalanine, 226 milligrams of aspartic acid and 54 milligrams of methanol. A six-ounce glass of milk would provide more phenylalanine and aspartic acid than this, and three ounces of beef would provide considerably more, as would wheat (Table 2). An eight-ounce glass of fruit or vegetable juice would provide somewhat more of the methyl esters than the aspartame, and a double martini would provide a great deal more methyl esters than aspartame. This amount of aspartame would represent about 5 percent of the average daily intake of phenylalanine, and less than that of the average intake of aspartic acid.

Some individuals will, in all probability, consume more than the estimated intake, and a few undoubtedly will consume much more. But as the dose level that was without effect in the safety studies was about 200 times the estimated consumption of 10 milligrams per kilogram of body weight per day, it will be difficult to conceive of an individual consuming enough aspartame to cause any adverse effects.

TABLE 2 Probable Consumption of Amino Acids from Aspartame

	Phe (mg)	Asp (mg)	-OCH ₃ (mg)
Aspartame (0.5 g)	280	226	54
Beef (3 oz)	653	1336	--
Wheat (3 oz)	490	541	--
Milk (6 oz)	310	443	--
Tomato juice (8 oz)			37
Gin (3 oz)	--	--	90

In summary, aspartame is an odorless, crystalline compound made up of substances that occur naturally in foods. It is about 200 times as sweet as sugar in taste tests, and has been tested extensively for safety in biological, toxicological, and other trials without effects from 100 to 200 times the estimated level of consumption.

75N-107

S 10177

June 10, 1974

CONGRESSIONAL RECORD — SENATE

CONFLICT OF INTEREST ON VITAMIN RECOMMENDED DIETARY ALLOWANCES

Mr. PROXMIRE. Mr. President, the Food and Drug Administration proposal to regulate safe vitamins and minerals as dangerous drugs if they exceed 150 percent of the so-called recommended daily allowance or recommended dietary allowance (RDA) of vitamins and minerals, is based on an arbitrary, unscientific, and tainted standard. The RDA standard is established by the Food and Nutrition Board of the National Research Council which is influenced, dominated, and financed in part by the food industry. It represents one of the most scandalous conflicts of interest in the Federal Government.

As author of a bill, S. 2801, which has 38 Senate cosponsors which would prevent the FDA from putting its regulations into effect next January I am particularly interested in this matter.

There are a dozen or more reasons why the so-called recommended daily allowance (RDA) is a capricious, unscientific, and illogical standard.

CONFLICTS OF INTEREST

First and foremost is the unconscionable conflict of interest of those on the Food and Nutrition Board which establishes it. The board is both the creature of the food industry and heavily financed by the food industry. It is the narrow economic interest of the industry to establish low official RDA's because the lower the RDA's the more nutritional their food products appear.

The board's industry liaison panels include breakfast food companies, candy

makers, soft-drink producers, baking firms, and chemical corporations.

The present chairman of the Food and Nutrition Board, for example, occupies an academic chair funded by the Mead-Johnson baby food company. He appeared at the FDA vitamin hearings not only as an FDA-Government witness but also on behalf of such firms and groups as Mead-Johnson and Abbott Laboratories.

He was also scheduled to appear on behalf of the Pet Milk Co. and Distillation Products. His research was funded to the tune of about \$40,000 by the FDA and he had additional Government grants of about \$90,000 in the year he appeared for the FDA.

In the latest—1974—edition of the Food and Nutrition Board's recommended daily allowances, most values that were changed were lowered from previous standards. There is a very simple and quite unscientific reason for this.

With low RDA's the food companies which advise the Food and Nutrition Board can then print tables on their food packages making their products appear to contain a higher level of nutrients than if higher or optimum levels were established. When milk and fruit together provide as much nutritional value as the breakfast food they are eaten with, one can see how ridiculously low and self-serving the new low RDA standards really are.

VALUES FLUCTUATE CAPRICIOUSLY

A second reason why the RDA standards are suspect is that they have fluctuated capriciously from year to year both in the nutrients listed and in the rec-

ommended daily allowance. For example, in the recommendations by the board for pantothenic acid, a B complex vitamin, in the period 1964-74, it was not on the 1964 list, was listed at 5 milligrams on the next list, was not on the third list, was back at 5 milligrams on the fourth list, was doubled to 10 milligrams on the fifth list, and was removed completely from the latest 1974 edition.

Is it a drug? Is it not a drug? Under the proposed FDA regulations, 10 milligram capsules would have been regulated as a drug after the second and fourth editions of the RDA's, as a food or a food supplement under the fifth change, and ignored after the 1974 list.

In the 1968 RDA list, there were 55 changes in value from the 1964 list, varying from 20 to 700 percent. The latest—1974—list shows similar subjective and unscientific variations. In the 1964-74 period the RDA's recommended by the Food and Nutrition Board for a child of 4 have varied by 100 percent for vitamin A, 230 percent for vitamin E, 700 percent for folacin, 150 percent for vitamin B-1, 122 percent for vitamin B-6, and 300 percent for vitamin B-12.

How can such an unstable standard be used to regulate vitamins? The RDA's are not scientific standards. They are little more than subjective, off-the-cuff and, in many cases, prejudiced values.

Mr. President, I ask unanimous consent that a table giving the RDA's for 16 nutrients as recommended by the Food and Nutrition Board since 1964, be printed in the Record.

There being no objection, the table was ordered to be printed in the Record, as follows:

TABLE 1.—RDA VALUES SINCE 1964 FOR 16 SELECTED NUTRIENTS

Nutrient and individual	A	B	C	D	E	F	Minimum to maximum variation of RDA (percent)	Latest variation and direction (percent)
Vitamin A, I.U.:							100	50
Child of 4.....	2,500.0	3,500.0	2,500.0	3,500.0	5,000.0	2,500.0	60	38
Pregnancy.....	6,000.0	8,000.0	6,000.0	8,000.0	8,000.0	5,000.0		
Vitamin E, I.U.:							230	70
Child.....	None	15.0	10.0	15.0	30.0	9.0	100	50
Pregnancy.....	None	30.0	30.0	30.0	30.0	15.0		
Vitamin C, mg.:							50	33
Child.....	50.0	60.0	40.0	40.0	60.0	40.0	67	
Pregnancy.....	100.0	100.0	60.0	60.0	60.0	60.0		
Folate/folicin, mcg.:							700	50
Child.....	None	50.0	200.0	200.0	400.0	200.0	700	
Pregnancy.....	None	100.0	800.0	800.0	800.0	800.0		
Vitamin B ₁ , mg.:							150	40
Child.....	.6	.8	.8	1.1	1.5	.9	70	18
Pregnancy.....	1.0	1.2	1.1	1.7	1.7	1.4		
Vitamin B ₂ , mg.:							67	35
Child.....	1.0	1.3	.9	1.2	1.7	1.1	33	25
Pregnancy.....	1.5	1.9	1.8	2.0	2.0	1.5		
Niacin, mg.:							82	40
Child.....	11.0	14.0	11.0	15.0	20.0	12.0	25	20
Pregnancy.....	16.0	21.0	15.0	20.0	20.0	16.0		
Vitamin B ₆ , mg.:							122	55
Child.....	None	1.0	.9	1.2	2.0	.9	25	
Pregnancy.....	None	2.0	2.5	2.5	2.5	2.5		
Vitamin B ₁₂ , mcg.:							300	75
Child.....	None	2.5	4.0	5.0	6.0	1.5	100	50
Pregnancy.....	None	5.0	8.0	8.0	8.0	4.0	100	0
Pantothenic acid, mg.:							100	0
Child.....	None	5.0	None	5.0	10.0	None	0	
Biotin, mg.:							87	47
Child.....	None	80.0	80.0	110.0	150.0	80.0	20	17
Pregnancy.....	None	150.0	125.0	150.0	150.0	125.0		
Magnesium, mg.:							100	50
Child.....	None	200.0	200.0	250.0	400.0	200.0	50	
Pregnancy.....	None	300.0	450.0	450.0	450.0	450.0	20	45
Iron, mg.:							100	0
Child.....	10.0	12.0	10.0	10.0	12.0	10.0	100	
Pregnancy.....	None	1.0	None	2.0	2.0	None	50	33
Copper, mg.:								
Child.....	None	None	None	None	15.0	15.0		
Zinc, mg.:								
Child.....	None	None	None	None	15.0	15.0		

A: 1964 FNB's RDA's Exh. O-14-1963.
B: 1966 FDA's RDA's in stayed regulations.
C: 1968 FNB's RDA's Exh. P-651.

D: 1970 FNB's RDA's introduced by Sorell Exh. G 351-3A.
E: 1973 FDA's RDA's in final regulations.
F: 1973, 74 FNB's RDA's, published 1974.

Mr. PROXMIRE. Mr. President, third. not only do the RDA's fluctuate capriciously and are established by those with overwhelming economic conflicts and self-serving interests, but there is a very considerable body of scientific evidence that the RDA's are ridiculously low. For example:

EXAMPLES OF LOW VALUES

Folacin. The RDA for folacin for some categories of individuals has varied by 700 percent in the last 10 years. It is now 400 micrograms for mature adults. The latest pronouncement cut the RDA for children in half. This has come at the very time the Canadian Government's nutritional survey found that half of all Canadians had "moderate deficiency" levels of folacin in their blood and that 10 percent of all Canadians were in the range of "high risk" deficiency.

There is strong evidence that the lack of folacin produces congenital deformities and increases the danger of accidental hemorrhage by fivefold. It is considered by some authorities as the most widespread deficiency in the United States, especially among pregnant women.

In light of such evidence, the RDA established for folacin by the Food and Nutrition Board appears to be dangerously low.

Vitamin B-6. The 1974 RDA for vitamin B-6 in 23-50-year-old females is 2 milligrams. But Dr. Paul Gyorgy, the eminent scientist who discovered vitamin B-6 recommended in 1971 that the general RDA for B-6 should be 25 milligrams a day or 12.5 times the present RDA. Women on the pill are especially subject to vitamin B-6 deficiency. Yet millions of women in the 23-50-year-old age group are told by the FDA and the Food and Nutrition Board that they can get a sufficient amount of B-6 at one-eighth the level which its discoverer recommends.

Vitamin C. There is now a very wide body of scientific evidence, in addition to the recommendation of Dr. Linus Pauling, the Nobel laureate, that the daily requirement for vitamin C is many times the 45 milligrams RDA now recommended by the Food and Nutrition Board.

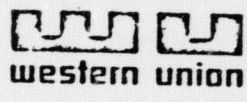
The double blind test performed at the University of Toronto by Professors Anderson, Reid, and Beaton in which half the subjects got 1 gram—1,000 milligrams a day—or 22 times the present RDA—and the other half a placebo, for 90 to 120 days—Canadian Medical Association Journal, September 1972—showed some amazing results. The number of illnesses, the duration of illnesses, the days confined at home, the days lost at work, and so forth, were all "statistically significantly" lower for the vitamin C as opposed to the placebo group.

The 45 milligrams RDA level now proposed by the Food and Nutrition Board is actually less than the traditional 50 milligram level said to be needed merely to prevent scurvy. But after next January, vitamin C in 100, 250, or 500 milligram tablets will be called a drug and regulated accordingly.

UNSCIENTIFIC STANDARD

The proposal to subject safe vitamins and minerals to regulation as drugs by the FDA if they are sold in quantities of 150 percent or more of the so-called RDA is a biased, unscientific, and capricious standard. At best the RDA's are only a "recommended" allowance at antediluvian levels designed to prevent some terrible disease. At worst they are based on the conflicts of interest and self-serving views of certain portions of the food industry. Almost never are they provided at levels to provide for optimum health and nutrition.

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SENATOR WILLIAM PROXMIRE
CAPITOL HILL DC 20510

I HAVE BEEN ASTOUNDED BY YOUR SPONSORSHIP OF THE SENATE BILL WHICH IS DESIGNED TO PROTECT FROM REGULATION BY THE FOOD AND DRUG ADMINISTRATION A SEGMENT OF US INDUSTRY THAT BILKS THE AMERICAN PUBLIC OF 500,000,000 TO 1 BILLION DOLLARS PER YEAR. AFTER SEEING THE AP REPORT OF YOUR SPEECH IN THE SENATE ON JUNE 10, I CAN UNDERSTAND YOUR SUPPORT OF THIS LEGISTRATION. THIS SPEECH IS OBVIOUSLY A MIXTURE OF HALF-TRUTH, UN-TRUTH AND OUT RIGHT FALSEHOODS BASED ON IGNORANCE. THE STATEMENTS REPORTED INDICATE THAT YOU OR YOUR SPEECH WRITERS KNOW NOTHING ABOUT NUTRITION, ABOUT THE RECOMMENDED DIETARY ALLOWANCES OF THE NATIONAL RESEARCH COUNCIL NOR ABOUT THE OBJECTIVES OF THE FOOD AND DRUG ADMINISTRATION IN REGULATING OVER-THE-COUNTER VITAMIN SALE. YOUR OBJECTIVE IN ATTEMPTING TO GAIN PUBLICITY THROUGH IRRESPONSIBLE DEFAMATION OF SCIENCES WHO ARE CONCERNED WITH THE HEALTH OF THE US POPULATION IS THE DEPLORABLE. AS A DEMOCRAT AND AS A CONSTITUENT OF YOURS I SHALL DO MY BEST TO INFORM THE PUBLIC OF YOUR EFFORTS TO CAPITALIZE ON THE SCARE TACTICS YOU ARE USING TO UNDER MINE THE EFFORTS OF A FEDERAL AGENCY TO PROTECT THE INTEREST OF THE US PUBLIC

A E HARPER CHAIRMAN OF THE COMMITTEE ON RECOMMENDED DIETARY ALLOWANCES 3447 EDGEHILL PARKWAY MADISON WISCONSIN 53705

20:44 EDT

MGMWSHT HSB

1 in this table in Senator Proxmire's speech of June 10, 1974,
2 complete with the footnote showing where each one of those
3 RDA figures came from?

4 MR. HOLSTEIN: Objection, Your Honor. I am sorry,
5 but I don't know how many times the witness must say the
6 same thing. He stated what he found objectionable in the
7 letter to my understanding.

8 JUDGE DAVIDSON: I agree, but I will allow him
9 to answer the question.

10 A I did not raise any question about the accuracy --

11 DR. ROBINSON: Your Honor, I cannot hear him.

12 A I did not raise a question about the accuracy of
13 the figures themselves. I raised a question about the statement
14 that these all represented recommended dietary allowances.
15 They do not.

16 Q Could you point out in the speech where it states
17 that all these figures represent dietary allowances. It was
18 my impression that the speech referred to the fact that
19 these figures came from a former Chairman of the Food and
20 Nutrition Board or from the Food and Drug or --

21 JUDGE DAVIDSON: All right. Let the witness look
22 at it and give you an answer. Don't keep going on.

23 THE WITNESS: I would like to ask for a 10-minute
24 recess to review this?

25 JUDGE DAVIDSON: Certainly.

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1 We will be back at 15 minutes after 4.

2 (Brief recess.)

3 JUDGE DAVIDSON: All right. Dr. Harper is ready.

4 Unless there is an objection, we can start.

5 CROSS EXAMINATION (Resumed)

6 BY DR. ROBINSON:

7 Q Yes, Dr. Harper --

8 JUDGE DAVIDSON: I think he had a question before
9 him that you asked, and he is ready to answer concerning
10 where he found in the document you handed him a reference
11 to the RDA's.

12 A I just want to give one example on Page S-10178,
13 Congressional Record, Senate, June 10, 1974, Mr. Proxmire
14 states examples of low values, folacin, the RDA for folacin
15 for some categories of individuals has varied by 700 percent
16 in the last 10 years. The table shows three columns that
17 are taken from the Food and Nutrition Board's recommended
18 dietary allowances, A, C, and F of Table 1 on Page S-10177.
19 A is the 1964 Food and Nutrition Board recommended dietary
20 allowances. There was no recommendation at that time.
21 C shows the recommendations for the child and for pregnancy
22 as 200 and 800 respectively. F shows the recommendation for
23 the child and for pregnancy as 200 and 800 micrograms
24 respectively, indicating that there was absolutely no change
25 whatever in the recommended dietary allowance for folic acid,

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1 and Senator Proxmire made the statement, and he included
2 the table, I assume, as illustration of this, and he stated
3 that there was a 700 percent variation.

4 Q Now, Dr. Harper, that sentence you referred to on
5 Page S-10178, does it state that the RDA varied with
6 respect to recommendations of the Food and Nutrition Board
7 or does it simply state that the RDA varied, period?

8 MR.HOLSTEIN: Objection, Your Honor, you have to
9 have some basis for the variance. You cannot talk about
10 apples and oranges.

11 JUDGE DAVIDSON: All right. I think the record
12 adequately reflects at this point exactly what the situation
13 is. Dr. Harper read it into the record, and I don't think
14 we have to quibble about whether it is proper variance or
15 an improper variance at this time. That is how it was
16 characterized, and unless there is some correction in what
17 you read Dr. Harper, I want to leave it the way it is.

18 THE WITNESS: I would be glad to make one minor
19 addition which is Senator Proxmire's conclusion in which he
20 says, on the basis of these analyses that he makes of the
21 more -- the so-called "RDA" is a biased, unscientific and
22 capricious standard on the basis of these variations that
23 he has cited.

24 (Pause.)

25 Q Dr. Harper, have you ever been in contact with

EXH. 0-936

Offered 11/17/75

NUTRIENT
REQUIREMENTS
OF
DOMESTIC
ANIMALS

NUMBER 10

Nutrient Requirements of Laboratory Animals

Second revised edition, 1972

CAT
GUINEA PIG
HAMSTER
MONKEY
MOUSE
RAT

Subcommittee on Laboratory
Animal Nutrition
Committee on Animal Nutrition
Agricultural Board
National Research Council

NATIONAL ACADEMY OF SCIENCES
Washington, D.C. 1972

Vitamin D

A requirement for vitamin D by the rhesus monkey has been established, but minimal and optimal dietary levels are not known. Gerstenberger (1938) produced rickets in 81 young rhesus monkeys and showed that sunlight or cod liver oil would induce healing of bony lesions. Kent *et al.* (1957) accidentally produced hypervitaminosis D in a colony of 558 rhesus monkeys (2.5–10 kg) by giving them 162,000 USP units of vitamin D/day for 3 months. The findings were weight loss, anemia, elevated blood urea nitrogen and serum calcium, and increased incidence of infections. Histological findings included calcium and iron deposits with foreign body type of inflammatory reactions in the kidneys, salivary glands, and lungs. The lesions regressed after the elimination of the vitamin D excess, and they were not observed after 1 year.

There is considerable evidence that all monkeys may not be alike in their requirements for a given form and level of vitamin D or both. Rhesus monkeys have been maintained on a variety of diets, including commercial diets based on vitamin D₂ (irradiated ergosterol) without evidence of bone disease. On the other hand, many species of New World monkeys (Family Cebidae) are susceptible to demineralization and fibrous dysplasia of bone, which seems to respond to a change from vitamin D₂ to vitamin D₃ (irradiated 7-dehydrocholesterol). Stare *et al.* (1963) presented a description of some of these lesions in the woolly monkey (*Lagothrix lagotricha*) maintained on diets supplying 100–200 units of vitamin D₂ daily. These lesions regressed with the lower level (100–200 units) of vitamin D₃ (O. W. Portman, unpublished data). Parenteral vitamin D₂ or D₃ at 50,000 units/week induced bone recalcification, kidney calcification, and kidney failure, and it was tentatively assumed on this basis that the inadequacy of vitamin D₂ in the woolly monkey is at the absorption level (O. W. Portman, unpublished data). Hunt *et al.* (1966) have described similar lesions in *Cebus albifrons* and marmosets (*Saquinis* sp.), and Lehner *et al.* (1966, 1967) observed lesions in squirrel monkeys (*Saimiri sciurea*), which appeared during the feeding of diets containing vitamin D₂ and regressed when vitamin D₃ was substituted for vitamin D₂. The latter workers demonstrated that 10 units of vitamin D₂/g of diet were inadequate, while as little as 1.25 units of vitamin D₃/g of diet prevented bone lesions. In January 1965, the use of vitamin D₃ in lieu of vitamin D₂ was initiated in semipurified diets for New World monkeys at the Oregon Regional Primate Research Center. Prior to that time some 200 squirrel

monkeys came to autopsy with a high incidence of gross or radiologically detectable bone lesions. Between January 1965 and June 1967, 305 squirrel monkeys had been autopsied and found to be apparently free of gross lesions. A particularly severe fibrous dysplasia was induced in 3 *Cebus* monkeys fed a diet containing vitamin D₂ and 10 percent hydrogenated coconut oil. These animals died in 5–8 months and had extremely flexible long bones (O. W. Portman, unpublished data). *Cebus* monkeys have, however, been maintained in apparent good health for over 5 years on diets including more unsaturated fats and vitamin D₂ (O. W. Portman, unpublished data). Hunt *et al.* (1967) have shown that vitamin D₂ increases calcium absorption in the deficient *cebus* monkey, whereas vitamin D₃ does not.

Vitamin E

The effects of vitamin E deficiency and the interrelationships of vitamin E requirements with the supply of other nutrients have been extensively studied in the rhesus monkey. Mason and Telford (1946, 1947) and Filer *et al.* (1949) presented the first studies of vitamin E deficiency in the rhesus monkey. Several comprehensive studies (Day and Dinning, 1956; Dinning and Day, 1957a,b) have been made of this muscular dystrophy syndrome. In addition, these workers have observed a vitamin E responsive anemia (Dinning, 1963; Porter *et al.*, 1962) and have proposed that vitamin E is a specific maturation factor for cells of the erythroid series as well as a factor influencing erythrocyte survival. Although the requirement for vitamin E depends in part on the level of unsaturated fat in the diet, Fitch and Dinning (1963) have shown that the deficiency can still be produced on a fat-free diet (Figure 5). They observed a mean requirement of 2.6 mg vitamin E/kg body weight for animals fed a diet containing 8 percent stripped lard and 3 percent cod liver oil and 0.7 mg for the fat-free diet. These calculations, based on creatine-to-creatinine excretion ratios, are equivalent to 1 mg vitamin E for approximately 3 g of polyunsaturated fatty acids. Horwitt (1962), on the basis of the nutritional supply of vitamin E to prevent *in vitro* hemolysis of adult human erythrocytes, proposed a value of approximately 1 mg vitamin E for each 1.2 g of linoleic acid in the diet as a minimum requirement.

Vitamin K

Two studies of attempts to induce vitamin K deficiency in rhesus monkeys have been described. Metta

Handwritten notes at bottom of page:
 2.6 mg/kg body weight
 40 IU/kg of D₃ at 5.7 IU/gm of oil
 400 IU/kg of D₃ at 5.7 IU/gm of oil

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1 JUDGE DAVIDSON: If, not until, if they do.

2 DR. DAVIS: Yes, right.

3 JUDGE DAVIDSON: Then it would be subject to anyone
4 who is interested in filing a comment and taking them to Court
5 again, if necessary. Right now that is not before me.

6 DR. DAVIS: I see.

7 JUDGE DAVIDSON: The only thing that is before me
8 are the stayed regulations.

9 DR. DAVIS: I see. My questions focus on the
10 scientific basis for the reduction from 1968 to 1974.

11 JUDGE DAVIDSON: We have been involved through that
12 so many times, and as far as I am concerned, if you want to
13 limit it to the scientific basis as to methodology used by
14 the Committee in reaching conclusions, fine, but as to the
15 extent of those conclusions, no.

16 DR. DAVIS: No, I am not talking about the extent
17 of the drop. I am talking about the scientific basis for the
18 present RDA.

19 JUDGE DAVIDSON: I don't see how that could be in
20 issue in this Proceedings. Now, what is in issue is, as I
21 have said before, the methodology used by the Board in reaching
22 the RDA.

23 DR. DAVIS: That is very much what my questions
24 are about.

25 JUDGE DAVIDSON: Then all you have to do is somehow

1 frame them so they don't involve the numbers.

2 DR. DAVIS: I see.

3 JUDGE DAVIDSON: Particularly between 1968 and 1974,
4 and we might be able to get the information.

5 DR. DAVIS: If I eliminate the word "reduction"
6 in my questions, does that do it?

7 JUDGE DAVIDSON: I don't know.

8 Ask your question.

9 CROSS EXAMINATION (Resumed)

10 BY DR. DAVIS:

11 Q My question would then be, would you agree that
12 the 1974 RDA is attributed to the work of Hodges and Baker
13 et al?

14 MR. KRULWICH: Objection.

15 JUDGE DAVIDSON: You see, you are not really
16 going into the area that we are concerned with, which is
17 the type of thing that went into making the 1968 RDA's to
18 the extent that Dr. Harper is familiar with them through his
19 work on both because the 1968 is what the regulations are
20 promulgated on.

21 DR. DAVIS: So, I may not inquire about the
22 scientific basis of the 1974 RDA's?

23 JUDGE DAVIDSON: That is not what I said.

24 DR. DAVIS: That is what I asked you.

JUDGE DAVIDSON: You keep asking the same thing.

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1 I keep giving you the same answer, and you keep asking me
2 the same thing. I am sure it is my own inadequacy and not
3 yours, sir.

4 DR. DAVIS: I just have to say I am confused. My
5 questions deal with the scientific basis of the 1974 RDA,
6 the method by which the 1974 RDA was developed.

7 JUDGE DAVIDSON: Is that different from the method
8 that developed the 1968?

9 DR. DAVIS: New papers have been --

10 JUDGE DAVIDSON: Ah, and that is the problem. You
11 only want to talk about the papers that were used and not
12 the methods.

13 DR. DAVIS: The methods that are in the papers.

14 JUDGE DAVIDSON: That is the problem. The problem
15 is we have a list of RDA's that were used by the FDA to
16 determine US RDA's, and it is the methodology involved in
17 determining the 1968 that is strictly before us. Now, if
18 you only want to talk about studies that were done subsequent
19 to 1968, they are relevant only to the extent that they show
20 what types of things the Committee would or would not
21 consider. The result of that is something which I have ruled
22 out.

23 (Pause.)

24 DR. DAVIS: I thought I saw a glimmer of hope that
25 I could get this in.

the range of 25 to 50 mg per day, and that the rate of absorption tends to go down as the amount consumed increases (Tr. 33184-33185).

Dr. Harper also agreed with Dr. Krikker that animal protein frequently carries iron that is more readily available than some of the iron from plant products (Tr. 33176). However, Dr. Harper explained that this would not necessarily increase the absorption rate since there are interactions that could reduce the availability of iron from other sources. It was on the basis of these factors that a figure of 10 percent for the absorption rate of iron was considered to be safe and proper (Tr. 33177). Finally, there is still extensive evidence of anemia (hemoglobin level lower than the standard for adequate health) in the United States. This is a major public health problem. Given this incidence of anemia, the Committee concluded that iron availability could not have been much higher than the absorption figure that they employed (Tr. 33177). The concern over anemia also resulted in the 50 percent increase in the RDA over a 10-year period (Tr. 33183). Thus, there is substantial evidence that the RDA for iron was set at a safe and appropriate level.

Dr. Krikker also raised questions with respect to whether the RDA for calcium is too high with respect to the nature of its relation to the intake of protein (Tr. 33237, Proposed Finding 23, 24). Dr. Harper explained that the reason the RDA for calcium was not lowered was because there is some indication of an imbalance that might arise from a high intake of protein, resulting in an increased loss of calcium, reflected by increased excretion in the urine (Tr. 33237). Therefore, the Committee decided not to lower the RDA for calcium until they can be certain that the calcium requirement of the American population is not being increased by the relatively high protein intake in the United States (Tr. 33237).

Dr. Krikker also expressed concern over the long-term effects of certain vitamins and minerals and the lack of adequate toxicological studies on long-term toxicity. The Commissioner shares this concern and agrees that more research is needed. In those cases where evidence indicated that high levels of exposure are not safe, he will take appropriate action. For example, the Commissioner has already promulgated regulations under §§ 250.109, 250.110, and 121.1134 (21 CFR 250.109, 250.110, and 121.1134) limiting, for reasons of safety, the amounts of vitamins A and D and folic acid which may be included in a preparation. The Commissioner recognizes that more research is necessary, and additional regulations will be promulgated as more information becomes available. (See also § 80.1(f) of the revised final regulations below, which incorporates certain safety-related restrictions upon use of vitamins and minerals.)

Dr. Krikker also proposed a number of findings based on questions she asked during her cross-examination and on

the eighth edition of the "Recommended Dietary Allowances" (1974) (Proposed Findings 25, 26, 28, 29, 31, 33, 37). However, these proposed findings were never related to the establishment of the RDA's during cross-examination of Dr. Harper. Therefore, there is no evidence on record as to what, if any, effect these matters might have on the scientific reliability of the RDA's. For example, Dr. Harper did agree that there is a difference in absorption and bioavailability of a nutrient depending upon its biological form, which varies with nutrients (Tr. 33222). Nevertheless, it was never established what effect, if any, this may have on the development or reliability of the RDA's. This is also true with respect to Dr. Krikker's proposed findings that excessive folic acid in foods may mask vitamin B₁₂ deficiency and that there is no "single minimum dietary requirement" or "single maximum safe intake" of a trace element.

Judge Davidson pointed out to Dr. Krikker this problem (of her asking questions that had no apparent relevance to the matter at hand) during her questioning with respect to iron: "Maybe I could help you if you would just put forth on the record what it is you are driving at." (Tr. 33169). Following this comment Judge Davidson helped Dr. Krikker relate her question concerning iron to the establishment of the RDA for iron by asking Dr. Harper if his impression of the RDA's "is affected by the subject matter that Dr. Krikker is trying to get into, the type of protein source, and if so, to what extent and how it entered into the deliberations of the Committee?" (Tr. 33176). While the connection between this area of inquiry and the Committee's deliberations over the RDA for iron was thereby established, a similar connection was not successfully established for the other areas of inquiry noted above. Nevertheless, the Commissioner has considered these points, and concludes that there is no evidence to support a conclusion that these factors raise a substantial question with respect to the scientific reliability of the RDA's.

11. 1974 revisions of NAS/NRC RDA's. Miles Laboratories filed an exception which asserts that the U.S. RDA's, which were developed in reliance on the 1968 NAS/NRC RDA's, should be revised pursuant to 1974 revisions of the NAS/NRC RDA's.

The Administrative Law Judge properly ruled that this matter was beyond the scope of the hearing, which was held to inquire into the process employed by the Food and Nutrition Board's Committee on Dietary Allowances in establishing the NAS/NRC RDA's to determine whether it was appropriate for FDA to use NAS/NRC figures as a basis for regulation. Moreover, the Commissioner has already stated in the May 28, 1975 document (40 FR 23243) that the changes made in the 1974 NAS/NRC RDA's are not of sufficient magnitude as they relate to overall public health to warrant similar changes in the U.S. RDA's at this time, but that it is reasonable to anticipate changes in the existing U.S. RDA's to reflect changes in the NAS/NRC

RDA's when the latter are next published.

The Commissioner has nevertheless reconsidered this issue. A review of the changes in the NAS/NRC RDA's indicates that they include a reduction (to 10) in the total number of age groupings for which values are given, reductions in the highest RDA values for each of six nutrients in each age grouping, a small increase in the value for riboflavin, and establishment of RDA's for zinc. The Commissioner notes that U.S. RDA's already exist for zinc and that they are consistent with NAS/NRC RDA's. He remains of the view that the changes in the 1974 NAS/NRC RDA's are not of sufficient magnitude to warrant changing the U.S. RDA's at this time.

The Administrative Law Judge also observed that this proceeding has been pending for 14 years and that the institution of further refinements in the U.S. RDA's at this time would only involve a needless further delay in development of final regulations (Report and Recommended Order on Limited Further Hearing, p. 10). The Commissioner agrees that the better course to follow is to establish the appropriateness and legality of the regulations at this time and make further modifications in the future when the need arises.

12. Allegations that Dr. Sebrell should have been produced as a witness. National Nutritional Foods Association, National Association of Pharmaceutical Manufacturers, and Solgar Co., Inc., took exception to the fact that Dr. Sebrell was not produced for cross-examination.

The Commissioner concludes that this exception is without merit. The Court of Appeals remanded this case "for the limited purpose of permitting reasonable cross-examination of Dr. Sebrell (or, if he is not available, some other qualified member of the Board) by Dr. Robinson or counsel for some other similarly interested participants" (504 F.2d 799). While the Commissioner was under no obligation to do so, he opened the hearing to all interested persons, and it is a group of these parties (not Dr. Robinson) which is now raising the exception to the witness produced by the agency. Dr. Robinson, who was primarily responsible for this remand, concurred in the calling of Dr. Harper in substitution for Dr. Sebrell and supported the Government's opposition to the motion which sought to prevent Dr. Harper from testifying (Tr. 32443).

The record shows that Dr. Sebrell was not interested in testifying (Exhibit P-1162), and FDA has no subpoena power to require his appearance. Moreover, Dr. Harper was eminently qualified. Dr. Harper is a professor of nutrition sciences and biochemistry and Chairman of the Department of Nutritional Sciences, University of Wisconsin. He is widely regarded as an expert in the field of human nutrition (Govt. Exhibit P-1162, P-1164; Tr. 32485). Dr. Harper was chairman of the Committee that was responsible for the 1974 RDA's and was a member of Dr. Sebrell's committee that formulated the 1968 RDA's (Tr. 32453). Dr. Hopper also

U.S. recommended daily allowances (U.S. RDA's) and permissible compositional ranges for dietary supplements of vitamins and minerals

Unit of measurement	Children under 4 years of age ¹			Adults and children 4 or more years of age			Pregnant or lactating women		
	Lower limit	U.S. RDA	Upper limit	Lower limit	U.S. RDA	Upper limit	Lower limit	U.S. RDA	Upper limit
Vitamins—Mandatory:									
Vitamin A..... International units.....	1,250	2,500	2,500	2,500	5,000	5,000	5,000	8,000	8,000
Vitamin D..... do.....	200	400	400	200	400	400	200	400	400
Vitamin E..... do.....	5	10	15	15	30	45	30	60	60
Vitamin C..... do.....	20	40	60	30	60	90	60	60	120
Folic acid..... do.....	.1	.2	.3	.2	.4	.4	.4	.8	.8
Thiamine..... do.....	.35	.70	1.05	.75	1.50	2.25	1.50	1.70	3.00
Riboflavin..... do.....	.4	.8	1.2	.8	1.7	2.3	1.7	2.0	3.4
Niacin..... do.....	4.5	9.0	13.5	10.0	20.0	30.0	20.0	20.0	40.0
Vitamin B ₆ do.....	.35	.70	1.05	1.00	2.00	3.00	2.00	2.50	4.00
Vitamin B ₁₂ Micrograms.....	1.5	3.0	4.5	3.0	6.0	9.0	6.0	8.0	12.0
Optional:									
Vitamin D..... International units.....				200	400	400			
Biotin..... do.....	.075	.150	0.225	150	300	450	300	300	600
Pantothenic acid..... do.....	2.5	5.0	7.5	5.0	10.0	15.0	10.0	10.0	20.0
Minerals—Mandatory:									
Calcium..... Grams.....	.125	.800	1.200	.125	1.000	1.500	.125	1.300	2.000
Phosphorus..... do.....	.125	.800	1.200	.125	1.000	1.500			
Iodine..... Micrograms.....	35	70	105	75	150	225	150	150	300
Iron..... Milligrams.....	5	10	15	9	18	27	18	18	60
Magnesium..... do.....	40	200	300	100	400	600	100	450	800
Optional:									
Phosphorus..... Grams.....							.125	1.300	2.000
Copper..... Milligrams.....	.5	1.0	1.5	1.0	2.0	3.0	1.0	2.0	4.0
Zinc..... do.....	4.0	8.0	12.0	7.5	15.0	22.5	7.5	15.0	30.0

¹ When labeled for use by infants, a dietary supplement shall contain not less than the lower limit designated for a nutrient in this set of columns, nor more than 100 percent of the infant U.S. RDA for a nutrient as prescribed in sec. 125.1(b) of this chapter except that the level of biotin, when used, shall be 0.05 mg daily recommended quantity.

² Optional for adults and children 4 or more years of age.

³ Optional for liquid products.

⁴ Optional for pregnant or lactating women. When present, the quantity of phosphorus may be not greater than the quantity of calcium.

(2) The U.S. Recommended Daily Allowances (U.S. RDA's) have been derived by the Food and Drug Administration from the "Recommended Dietary Allowances," published by the Food and Nutrition Board, National Academy of Sciences/National Research Council, and are subject to amendment as more

knowledge on human nutrient requirements becomes available.

(3) For determining the percentage of the U.S. RDA present in a dietary supplement, the quantitative content of the following vitamins shall be calculated in terms of the following chemically identifiable reference forms:

Reference form

Vitamin	Name	Empirical formula	Molecular weight
Vitamin C.....	L-Ascorbic acid.....	C ₆ H ₈ O ₆	176.2
Folic acid.....	Pteroyl mono-L-glutamic acid.....	C ₂₀ H ₂₆ N ₇ O ₆	441.41
Thiamine.....	Thiamine chloride hydrochloride.....	C ₁₂ H ₁₇ ClN ₄ OS·HCl	337.28
Riboflavin.....	Riboflavin.....	C ₁₇ H ₂₀ N ₄ O ₆	376.37
Niacin.....	Nicotinic acid.....	C ₆ H ₅ NO ₂	123.11
Vitamin B ₆	Pyridoxine.....	C ₈ H ₉ NO ₃	169.18
Vitamin B ₁₂	Cyanocobalamin.....	C ₆₃ H ₈₈ CoN ₁₄ O ₁₄ P	1,355.40
Biotin.....	D-Biotin.....	C ₁₀ H ₁₆ N ₂ O ₃ S	244.31
Pantothenic acid.....	D-Pantothenic acid.....	C ₉ H ₁₇ NO ₆	219.23

(4) In addition to the nutrients listed in paragraph (d)(1) of this section, other vitamins and minerals recognized as essential or probably essential in human nutrition in their biologically active forms but for which no U.S. RDA's have been established are: vitamin K, choline, and the minerals chlorine, chromium, fluorine, manganese, molybdenum, nickel, potassium, selenium, silicon, sodium, tin, and vanadium.

(e) *Exemption from limitations on inclusion of ingredients and from maximum potency restrictions for certain dietary supplements.* (1) Pursuant to section 411(a)(1) of the act, the limitations established by paragraphs (b) and (d) of this section and by § 125.2(b)(5) of this chapter with respect to the inclusion of vitamins, minerals, and other ingredients in dietary supplements, and the maximum limits on potency established by paragraphs (c) and (d) of this section shall not apply to a food for special dietary use, defined in § 125.1(a)(1) of

this chapter, which is or contains any vitamin or mineral and which complies with the following criteria:

(i) The preparation is intended for ingestion in tablet, capsule, or liquid form, or, if not intended for ingestion in such a form, does not simulate and is not represented as conventional food and is not represented for use as a sole item of a meal or of the diet; and

(ii) The preparation is not represented for use by individuals in treatment or management of specific diseases or disorders, by children, or by pregnant or lactating women.

(2) For purposes of paragraph (e)(1) of this section: a food shall be considered as intended for ingestion in liquid form only if it is formulated in a fluid carrier and it is intended for ingestion in daily quantities measured in drops or similar small units of measure; and the term "children" means individuals who are under the age of 12 years.

(3) The exemption provided by section 411(a)(1) of the act and paragraph (e)(1) of this section does not apply to minimum potency requirements established by this section. Whenever a vitamin or mineral for which a U.S. RDA has been established is included in a dietary supplement, the supplement shall provide in the recommended daily quantity at least the lower potency limit for the vitamin or mineral established by the table in paragraph (d)(1) of this section.

(4) The exemption provided by section 411(a)(1) of the act and paragraph (e)(1) of this section does not apply to restrictions on maximum potency imposed by the act or by regulations for reasons of safety under paragraph (f) of this section.

(f) *Restrictions on maximum potency of vitamins and minerals for reasons of safety.* Restrictions of the maximum potency of a vitamin or mineral may be imposed for reasons of safety by the act or by regulation. For convenience, certain restrictions are cross-referenced below:

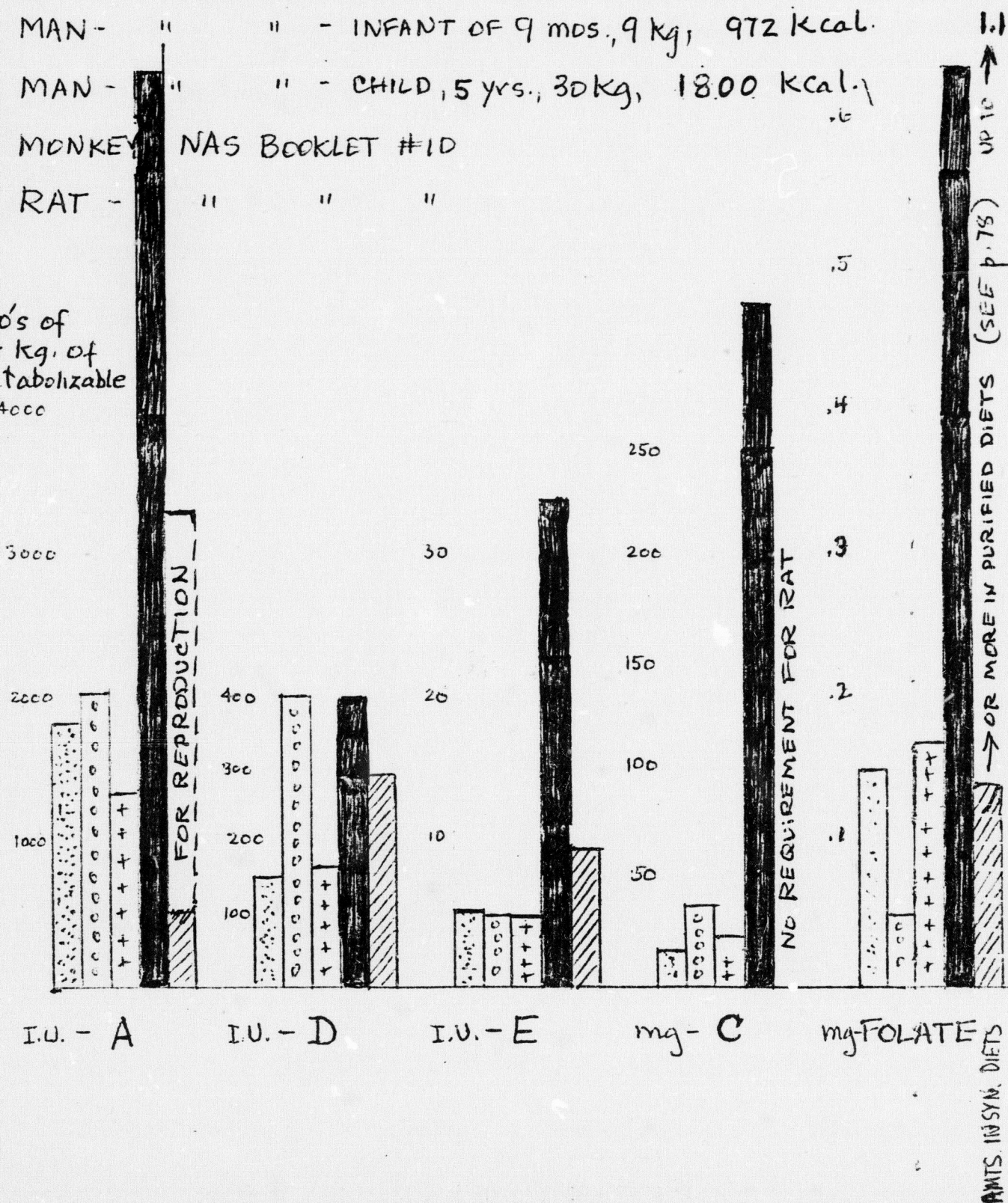
- (1) Vitamin A—See § 250.109.
- (2) Vitamin D—See § 250.110.
- (3) Folic acid—See § 121.1134.
- (4) Iodine—See §§ 121.1073 and 121.1149.
- (5) Copper—See § 121.101(d)(5).
- (6) Fluorine—See § 121.10.
- (7) Potassium—See § 201.306.

(8) Any vitamin or mineral which is included in a dietary supplement and which is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown to be safe under the conditions of its intended use is a food additive within the meaning of section 201(s) of the act, and pursuant to sections 402(a)(2)(C)

NUTRIENT RE

- $\frac{RDA}{2.7}$ $\square$ MAN - NAS/FNB 1974 - ADULT 70 kg. 2700 Kcal.
- $\frac{RDA}{0.97}$ $\square$ MAN - " " - INFANT OF 9 mos., 9 kg, 972 Kcal.
- $\frac{RDA}{1}$ $\square$ MAN - " " - CHILD, 5 yrs., 30 kg, 1800 Kcal.
- $\frac{Amt. kg. diet}{3.6}$ $\blacksquare$ MONKEY NAS BOOKLET #10
- $\frac{Amt. kg. diet}{3.6}$ $\square$ RAT - " " "

3.6 = 1000's of
Kcal per kg. of
diet (metabolizable
energy) 4000

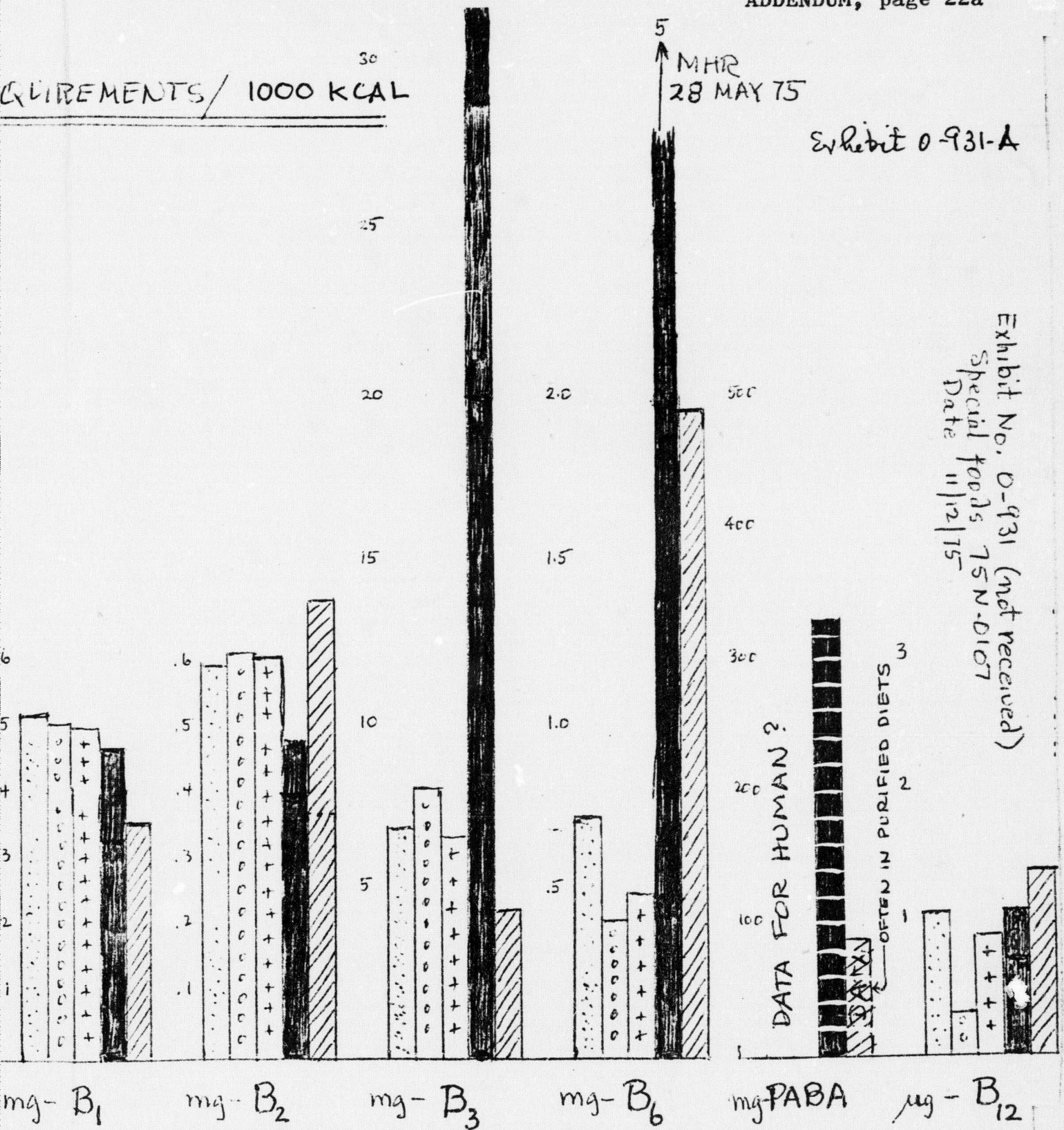


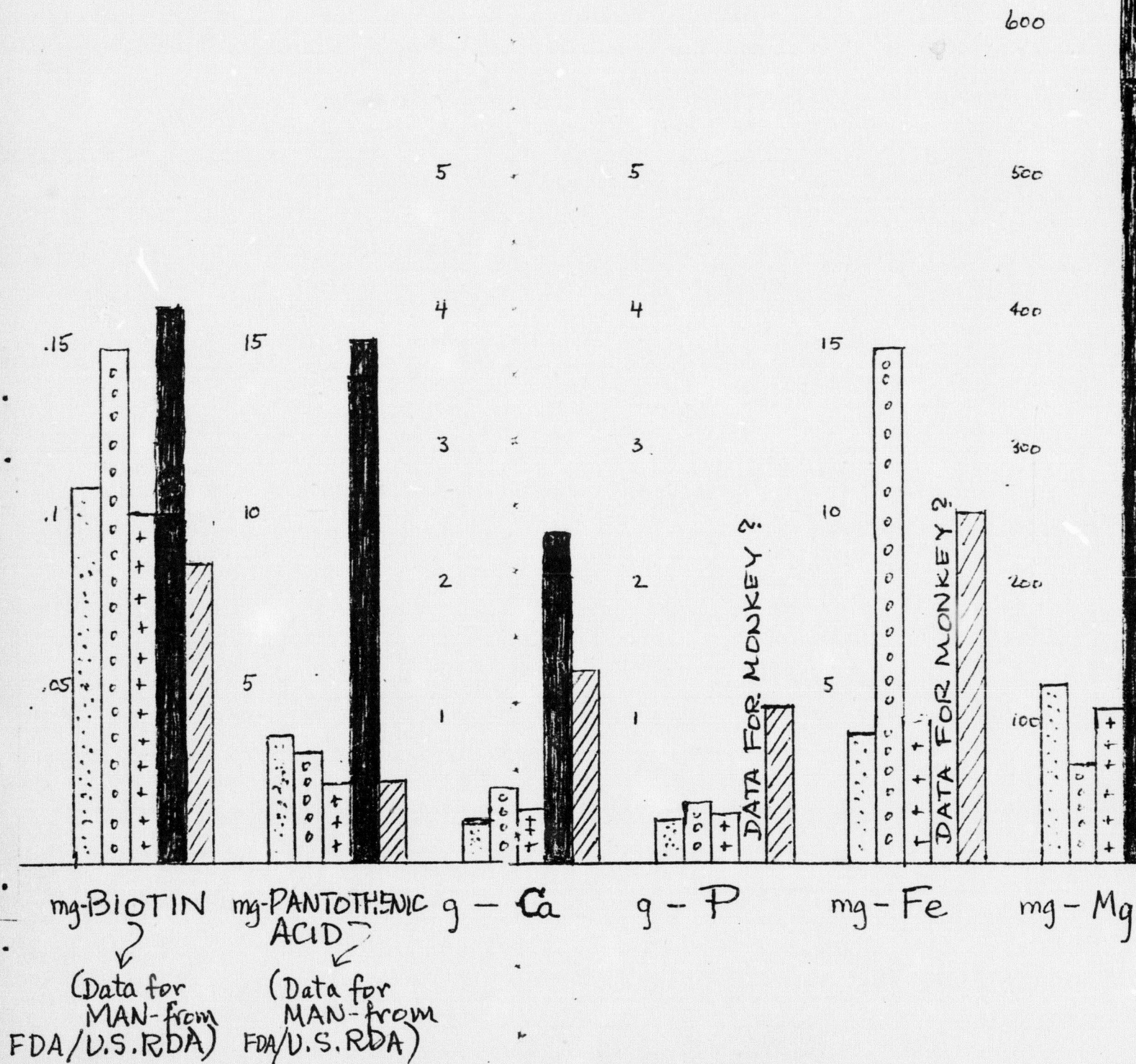
REQUIREMENTS / 1000 KCAL

MHR
28 MAY 75

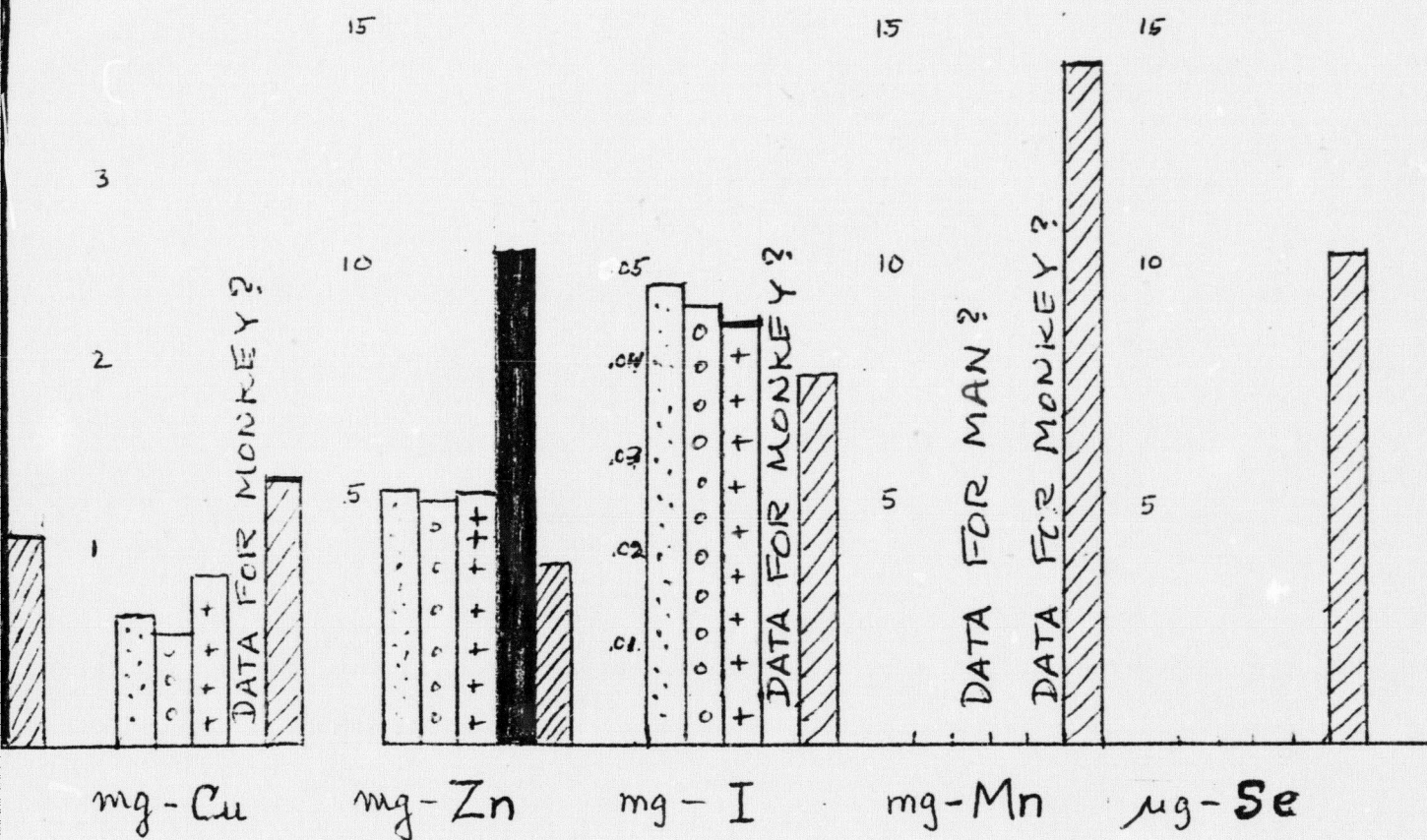
Exhibit 0-931-A

Exhibit No. 0-931 (not received)
Special foods 75N-D107
Date 11/12/75





28 MAY 1975



MITR

0-932-A

offered 11/14/75

NORMALIZED DISTRIBUTION CURVES

I. GAUSSIAN OR "NORMAL"

$$y(x) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left(\frac{-x^2}{2\sigma^2}\right)$$

II. POSSIBLE NON-GAUSSIAN

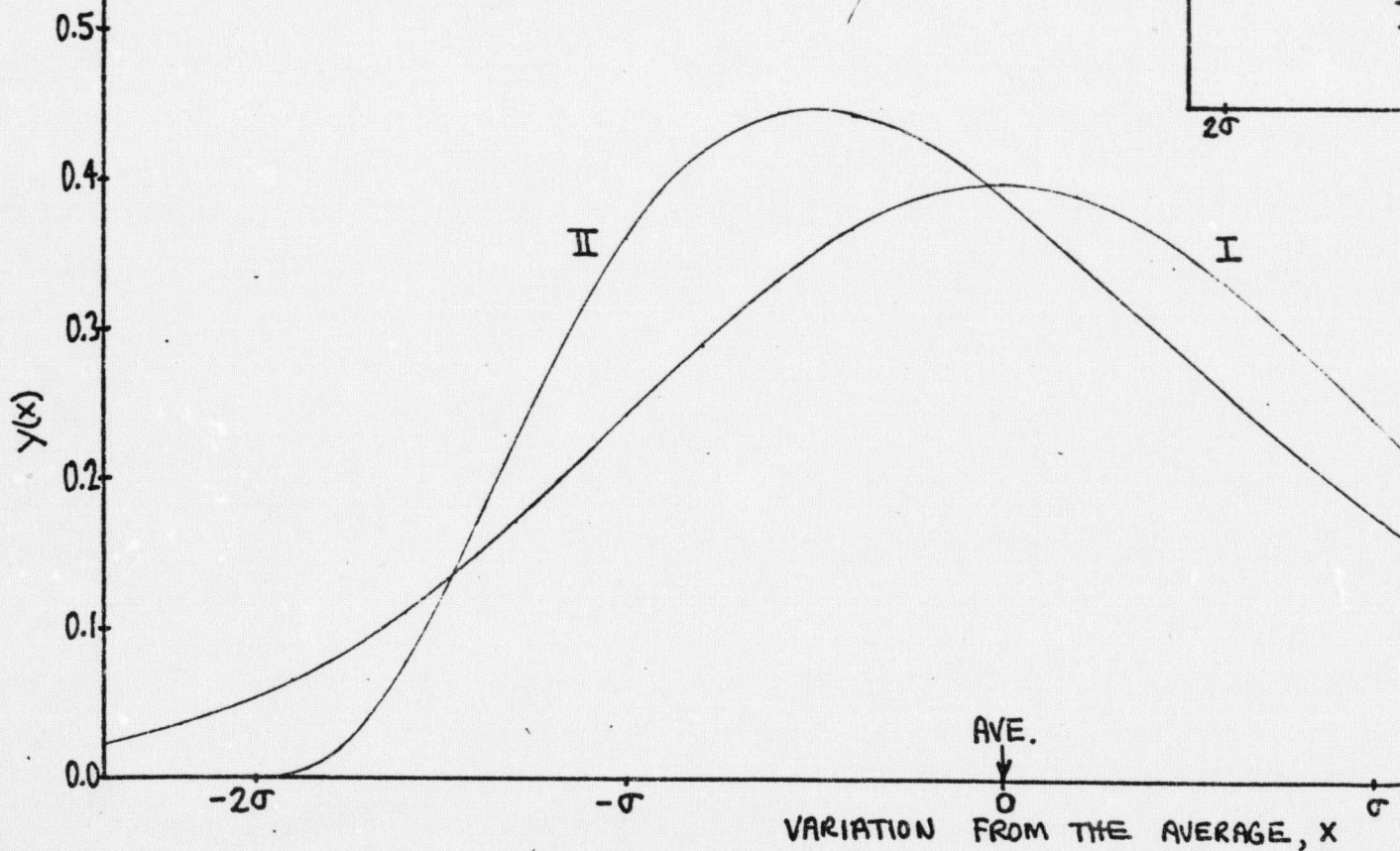
$$y(x) = \frac{8}{3\sigma} \left(\frac{x}{\sigma} + 2\right)^3 \exp\left(\frac{-2x}{\sigma} - 4\right)$$

BOTH CURVES HAVE

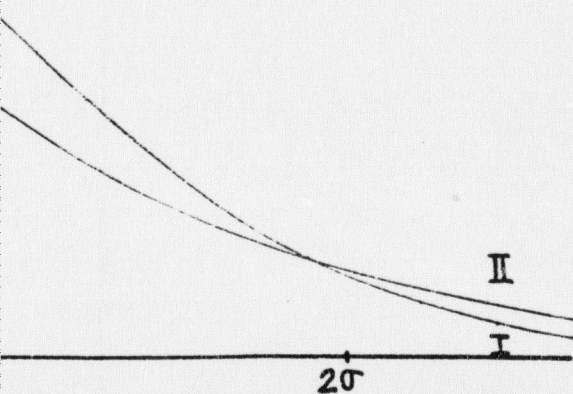
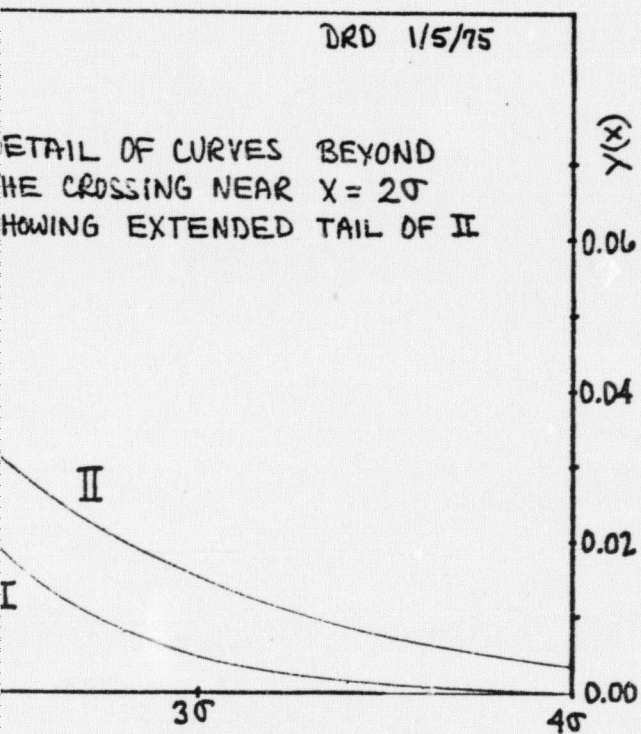
EQUAL AREAS, 1.0 IN σ UNITS

EQUAL AVERAGES, $x = 0$

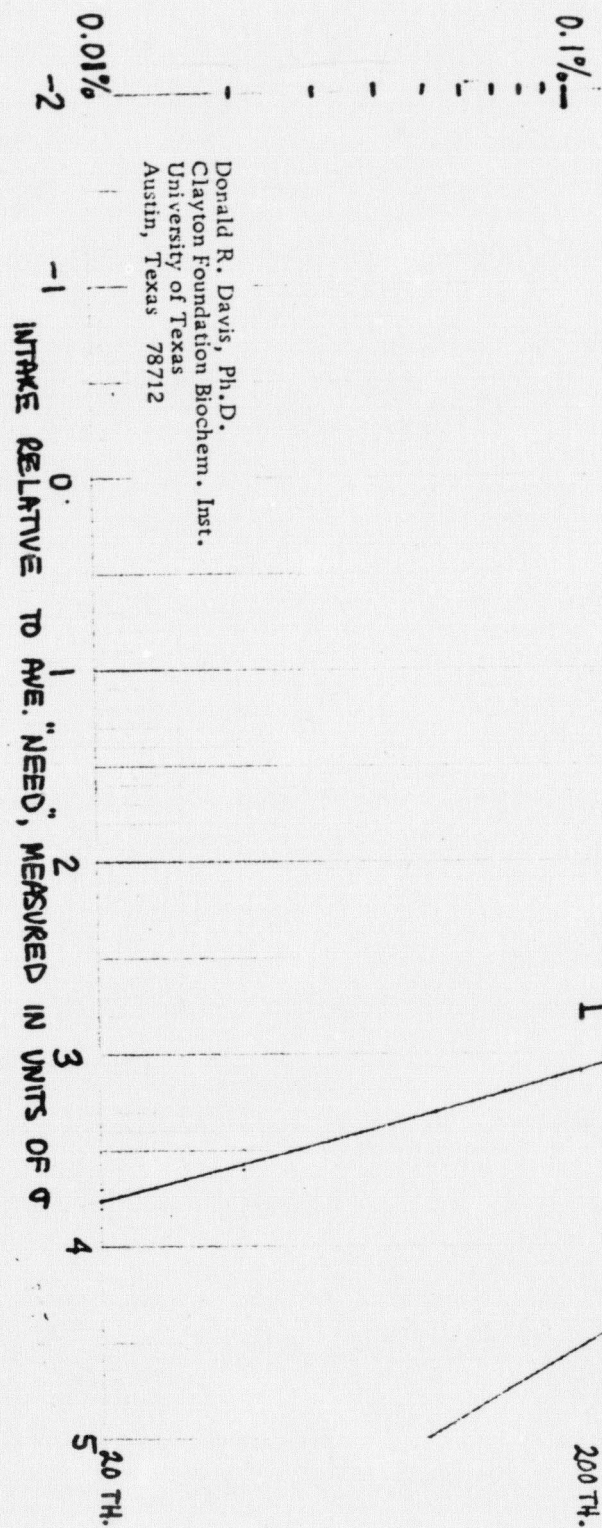
EQUAL STANDARD DEVIATIONS, σ



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 Foundation Biochemical Inst.
 University of Texas
 Austin, Texas 78712

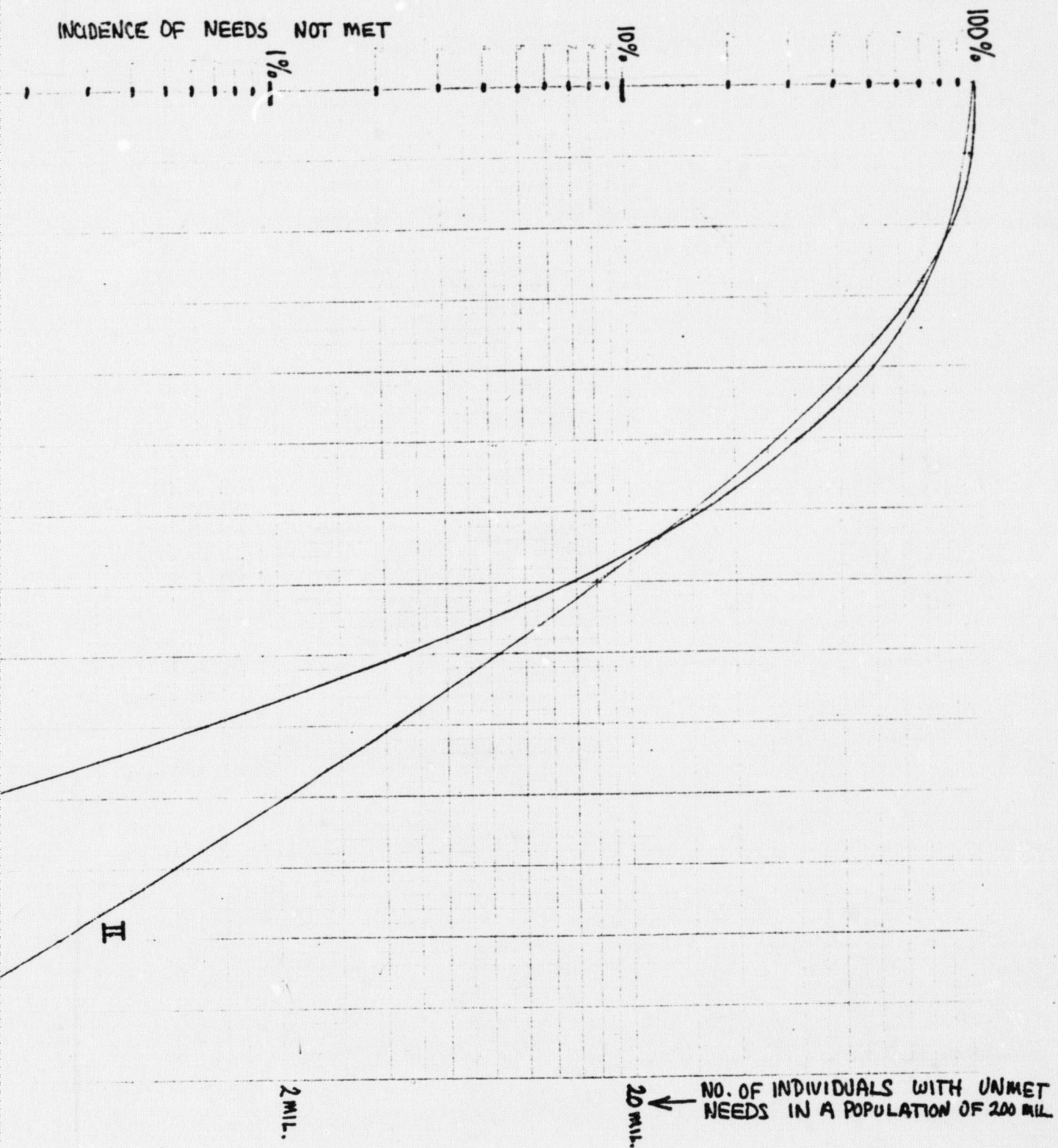


0932-B



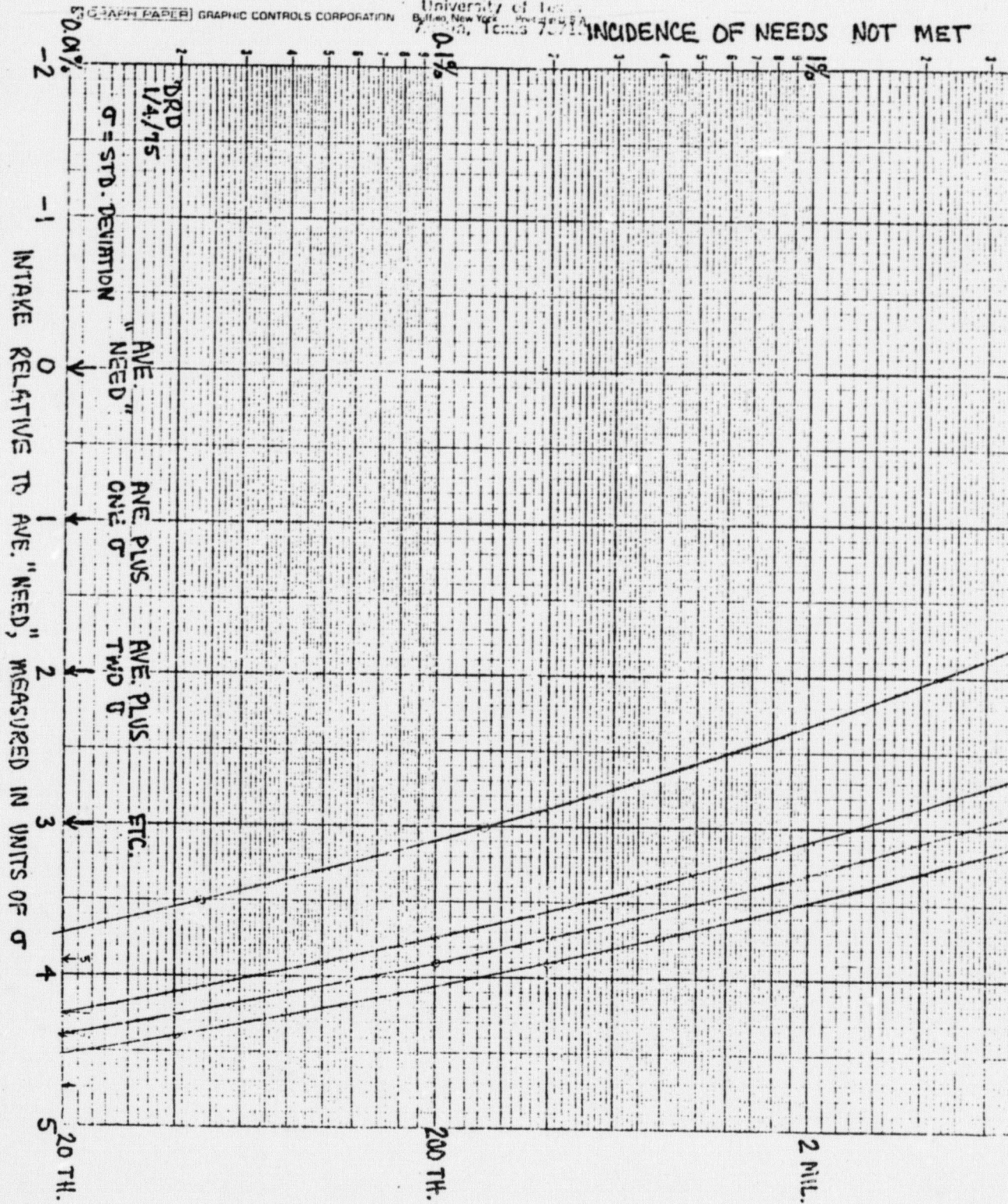
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24. 0932-B



D-932-C

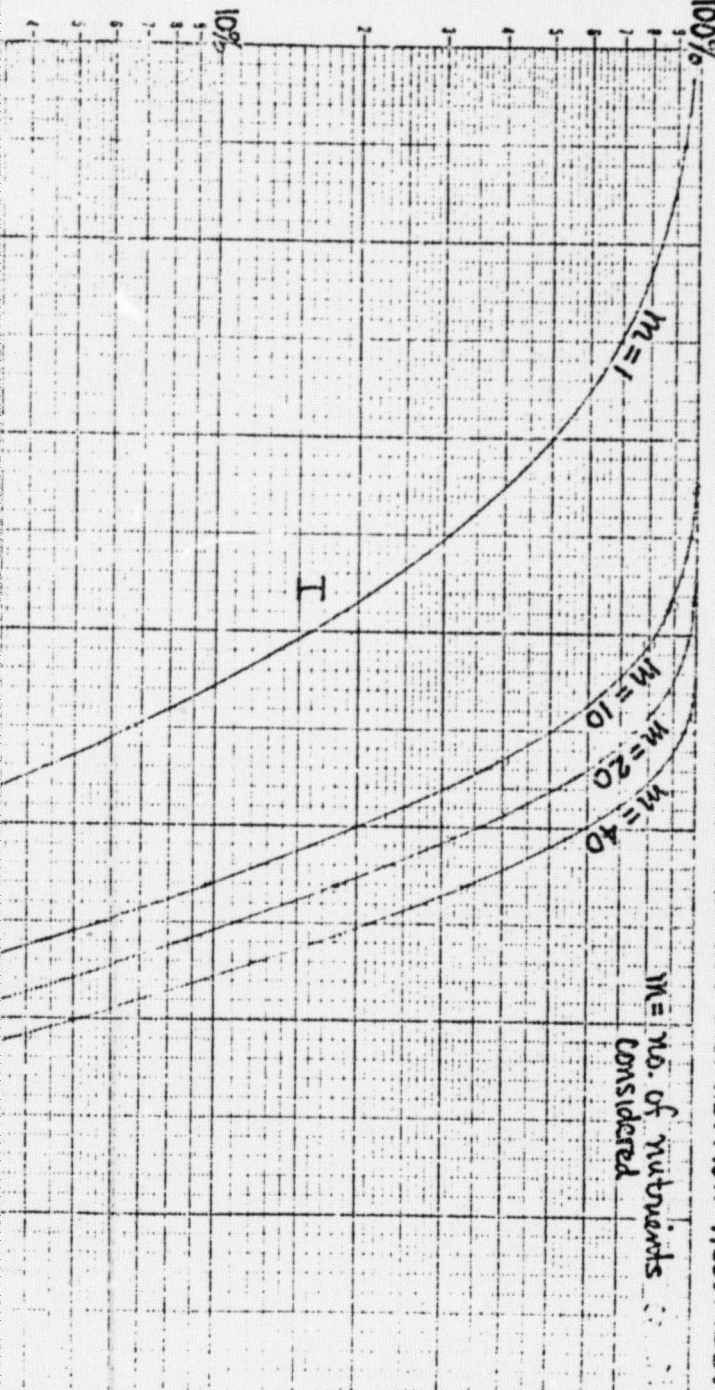
DONALD R. DAVIS, Ph. D.
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 University of Texas
 Dallas, New York
 Dallas, Texas 75271



22A. D-932C

(3)

SEMI-LOGARITHMIC 4 CYCLES X 70 DIVISIONS AD 0843-67



NO. OF INDIVIDUALS WITH UNMET NEEDS IN A POPULATION OF 200 MIL.
 20 MIL. →

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DRD
1/5/75

Ave.
"NEED"

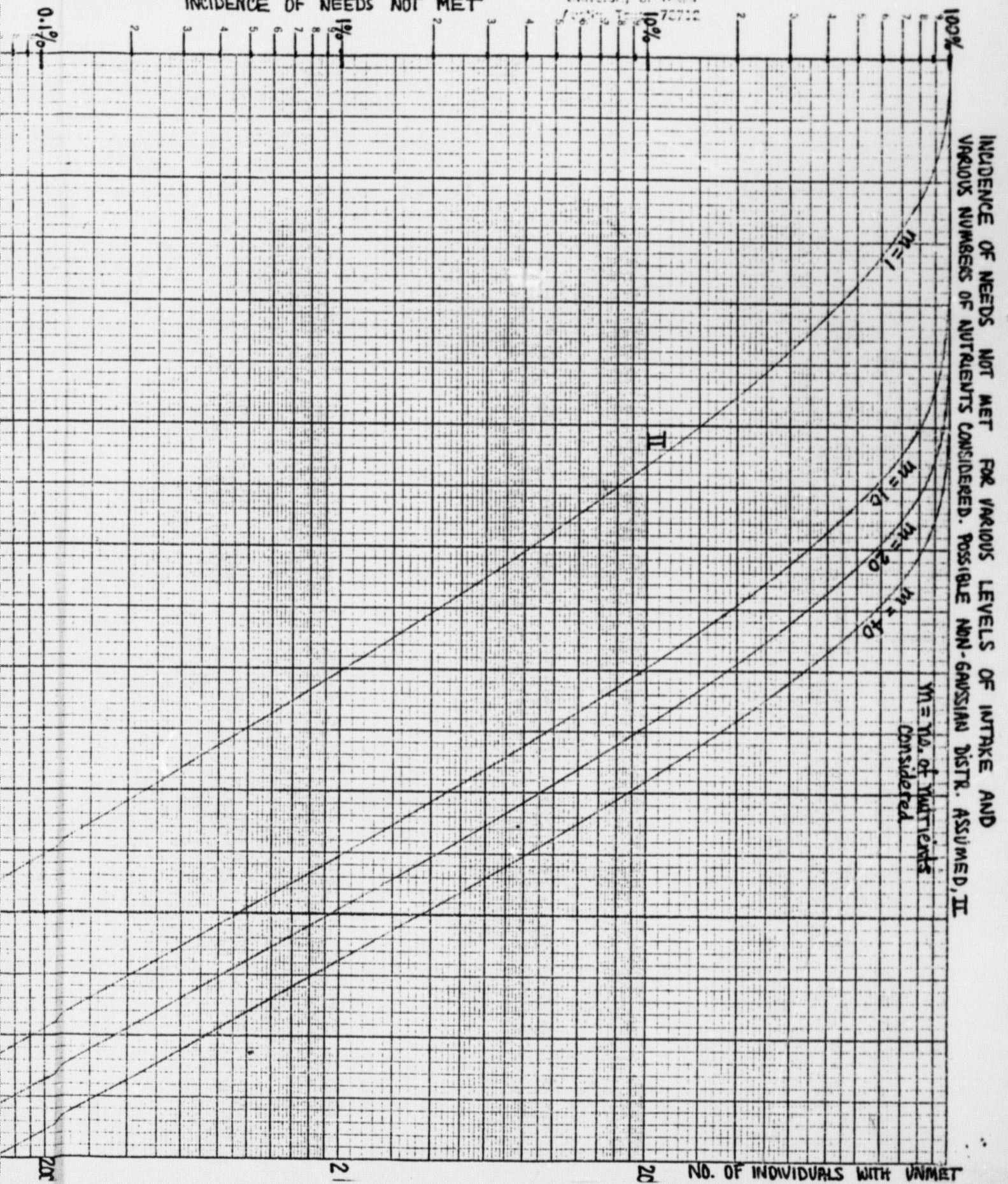
0.01%
-2
-1
0
1
2
3
4
5
6
7
20

INTAKE RELATIVE TO AVE. "NEED", MEASURED IN UNITS OF σ

SEMI-LOGARITHMIC 46 6013
4 CYCLES X 7 DIVISIONS
KEUFFEL & ESSER CO.

DONALD E. DAVIS, Ph. D.
Foundation Biochemical Institute
University of Texas
Austin, Texas 78712

INCIDENCE OF NEEDS NOT MET





1 as an actual situation. If you want to put this in terms of
2 a statistical distribution, and if you are studying a series
3 of variables in a statistical distribution under the very
4 restrictive conditions that you are setting, one can just
5 follow the theoretical problem to its ultimate limits, yes,
6 and one gradually sees that there is a probability of an
7 increase in the numbers, right, but I would like to be
8 absolutely clear that this is a purely hypothetical situation
9 that we are dealing with.

10 Q It is not hypothetical, Dr. Harper, is it, in the
11 sense that whatever the RDA's are set at for each nutrient
12 that RDA meets a certain percentage of the needs of the
13 population? It may be 99.99 percent, but it meets a
14 certain percentage.

15 A And it might be 100 percent, and then the whole
16 calculation would be meaningless. The food intake of the
17 population may exceed the recommended allowance by a
18 considerable amount, and then the whole calculation is
19 meaningless. That is what I am trying to get at. I can
20 set up all kinds of hypothetical situations where I can
21 get an answer that I would like to have.

22 Q Dr. Harper, isn't it true that the Food and
23 Nutrition Board has recently decided that there are 10
24 nutrients for which there is a risk of deficiency in the
25 American population, and they have decided that these



1 nutrients probably ought to be added to wheat and other
2 cereal products?

3 MR. JOHNSON. Objection.

4 JUDGE DAVIDSON: Overruled. If the doctor knows,
5 he may answer.

6 A I have not seen such a statement.

7 Q You have not seen the 1974 proposed cereal
8 fortifications?

9 JUDGE DAVIDSON: All right. Now, excuse me. You
10 are arguing with him, I think. You asked him a question
11 which had really nothing to do with what we are talking about.
12 I let him answer it. He said that he had not seen it, and now
13 you want to ask him again whether he has seen it.

14 DR. DAVIS: Well, I am kind of dumbfounded, frankly.

15 JUDGE DAVIDSON: Well, maybe that is true, but as
16 I said before, that is why I don't like you putting things
17 in your question that are supposedly facts, because the
18 witness can't accept something he doesn't know about. Yet,
19 it stays in the record.

20 DR. DAVIS: Could I ask a more general question,
21 then?

22 JUDGE DAVIDSON: On the same area?

23 DR. DAVIS: Yes.

24 JUDGE DAVIDSON: Of something that isn't really
25 involved in this Proceeding, something new that we --

33119

1 DR. DAVIS: Oh, no.

2 JUDGE DAVIDSON: Well, what are you talking about?

3 DR. DAVIS: I am trying get at the point that
4 there may be a sizable number of nutrients for which there
5 is evidence of risk of deficiency in the American food supply,
6 and therefore this calculation is not irrelevant.

7 Q Dr. Harper, are you --

8 JUDGE DAVIDSON: Wait a minute.

9 DR. DAVIS: I am sorry.

10 JUDGE DAVIDSON: I will let him answer that
11 question, that's all, the way you just gave it to me.
12 Do you agree or disagree with that statement?

13 THE WITNESS: It could be irrelevant.

14 DR. DAVIS: It could be irrelevant?

15 THE WITNESS: Yes. I would like to make the point
16 that when there was pellagra in this country, I am sure
17 they did not have to go through all this statistical
18 manipulation in order to know enough to include niacin in
19 the diets or to consider niacin as a source of fortification
20 of foods. It took the knowledge that the disease existed,
21 the knowledge that the food supply was inadequate and the
22 knowledge of the amount required to prevent the signs from
23 developing, and pellagra disappeared from the country, and
24 I am sure it was done without all of this kind of statistical
25 manipulation.